

**Long-term pharmacotherapy of adults with  
Attention-Deficit/Hyperactivity Disorder (ADHD):  
A literature review and clinical study**

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## List of papers

The thesis is based on the following three papers:

### **Paper I based on Study I.**

Fredriksen M, Halmoy A, Faraone SV, Haavik J. Long-term efficacy and safety of treatment with stimulants and atomoxetine in adult ADHD: A review of controlled and naturalistic studies. *Eur Neuropsychopharmacol* 2013;23:508-27.

### **Paper II based on Study II.**

Fredriksen M, Dahl AA, Martinsen EW, Klungsøyr O, Faraone SV, Peleikis DE. Childhood and persistent ADHD symptoms associated with educational failure and long-term occupational disability in adult ADHD. *ADHD Atten Def Hyp Disord* (accepted for publication, January 2014).

### **Paper III based on Study III.**

Fredriksen M, Dahl AA, Martinsen EW, Klungsøyr O, Haavik J, Peleikis DE. Effectiveness of one-year pharmacological treatment of adult attention-deficit/hyperactivity disorder (ADHD): An open-label prospective study of time in treatment, dose, side-effects and comorbidity. *Eur Neuropsychopharmacol*, submitted 2014.

## Abbreviations

ADHD	attention-deficit/hyperactivity disorder
AMP	amphetamine
ASRS	adult ADHD self report scale
ATX	atomoxetine
CGI	Clinical Global Impression rating scales
CS	central stimulants
DSM	Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association
GAF	Global Assessment of Functioning scale
GSI	Global Severity Index (derived from SCL-90)
HD	hyperkinetic disorder
ICD	World Health Organization International Classification of Diseases
MINI	Mini International Neuropsychiatric Interview
MPH	methylphenidate
OR	odds ratio
PCT	placebo controlled trials
RCT	randomized controlled trials
SCL-90	Symptom Check List 90
WURS	Wender Utah Rating Scale



## Summary of the thesis

**Background:** ADHD in adulthood is associated with a wide range of clinical and psychosocial impairments, and the number of adults referred for medical treatment is considerable.

**Aims:** The overall purpose of this thesis was to study clinically relevant aspects of long-term medical treatment of patients with adult ADHD. To achieve this, three aims were defined: 1) To systematically review the literature on long-term ( $\geq 24$  weeks) pharmacological treatment of adults with ADHD (Study I); 2) To explore educational and occupational status as functional outcomes in previously not medicated adult ADHD patient (Study II); and 3) To assess outcomes of a 12 months first time medical treatment period of such patients (Study III).

**Materials and methods:** In Study I we reviewed electronic databases to identify original studies of long-term effects of stimulant therapy in adults. Studies II and III were conducted on a sample of patients recruited at a specialized outpatient clinic for adult ADHD patients.

Study II was a cross-sectional investigation of the impact of retrospectively retrieved childhood dimensional ADHD symptoms and characteristics as well as present state ADHD symptoms on the current level of basic education and current work status in medication-naïve adults with ADHD.

Study III was an open-labeled prospective observational study of the 250 adults consecutively included and described in Study II, who received methylphenidate according to current guidelines with a titration-regime for 6 weeks, followed by a flexible-dose-regime. Patients, who did not respond or were non-tolerant for methylphenidate, were shifted to amphetamine or atomoxetine.

**Results:** Study I: Most of published pharmacological studies reviewed were short-term randomized placebo-controlled trials (RCTs); four trials had intermediate duration between 24 weeks and one year. In contrast to findings in the short- and intermediate term ( $< 24$  weeks) trials, where drug effects are well established, long-term effects ( $> 24$  weeks) of medication on symptoms and functional outcomes, as well as side effects or complications, were less studied. We identified some open label extension studies from short term RCTs ( $n = 10$ ) that evaluated outcome up to 52 weeks, except for one study on atomoxetine of three years.

Study II: High number of childhood hyperactive-impulsive symptoms and overall severity of childhood ADHD-symptoms were significantly associated with high drop-out rates from school (OR = 3.0), while persisting ADHD inattentive symptoms (OR = 2.5) and comorbid mental disorders (OR = 1.6) in adulthood were more related to the proportion with long-term work disability.

Study III: A total of 232 patients (93%) starting medical treatment completed examination at 12-months, and 70% of them persisted on medication, most commonly methylphenidate, while 30% had discontinued medication. Longitudinal analyses showed significant associations between sustained improvement of symptoms and global functioning measures, and staying on medication. Comorbid mental disorders and adverse effects of medication were related to both lower effectiveness, and reduced adherence to treatment. No serious adverse events were observed.

**Conclusions:** Study I: The literature on long-term effects of ADHD-medication in adults was scarce and primarily naturalistic. The results suggested that pharmacological treatment of ADHD leads to less symptoms, better self-esteem, higher educational levels and occupational status, fewer accidents, and less delinquency compared to non-treatment, and medication was well tolerated.

Study II: Higher levels of untreated childhood ADHD hyperactive-impulsive symptoms and overall severity of ADHD symptoms were associated with lower level of basic education. Persisting ADHD inattention symptoms and comorbid mental disorders in adulthood were more related to long-term work disability.

Study III: Among stimulant-naïve adults with ADHD 70% continued on medication at one-year follow-up, and treatment with stimulants or atomoxetine was associated with a clinically significant reduction in ADHD symptoms and mental distress, and improvement on measure of global function.

In a general clinical setting one-year treatment with ADHD medications were associated with significant improvements of patients who continued on medication compared with those who discontinued. Given the nature of an open-label uncontrolled design, this calls for more controlled studies on medical treatment in a longer time perspective.

# 1. Background

## *1.1. Clinical environment and study inception*

Treatment with psychostimulants such as methylphenidate and amphetamine of adult patients with attention-deficit/hyperactivity disorder (ADHD) according to the DSM-IV classification (American Psychiatric Association 1994), or hyperkinetic disorder in the ICD-10 (World Health Organization 1993) which is the official psychiatric classification system of Norway, was first allowed in Norway in 1997. Until 2005 special permission was required from the health authorities for prescription to patients of all ages. From that year the control routines became less rigid, but individual permission was still necessary for prescription of psychostimulants to patients with ADHD.

The Psychiatry of Vestfold County established an ADHD-team in 1997, in order to deliver specialized health services to adults ( $\geq 18$  years) with ADHD. This team has been operating continuously as a centralized outpatient service for adults with ADHD-like symptoms or impairments. The author of this thesis has been a member of this team since 2001.

An increasing number of patients have been referred to the services. During the last three years about 500 new patients have been evaluated each year, and the majority have been treated for ADHD. The current study was planned in 2007, when evidence was scarce for long-term benefits of medical treatment of ADHD in adults. However, due to needs of funding and formal approvals the study started in 2009. Following an application to the Norwegian Council for Mental Health the author received a PhD-grant from the Norwegian Extra Foundation for Health and Rehabilitation. Since this study started 2009, several studies addressing aspects of the research questions raised in the current project have been published. Thus, in order to provide novel contributions, some of the research themes in the primary protocol have been modified.

## **1.2. Basic characteristics of ADHD**

### **1.2.1. Childhood ADHD**

ADHD according to the DSM-IV-TR classification (American Psychiatric Association 2000) is a common childhood mental disorder with a prevalence varying from 2-10% among children (Heiervang et al. 2007, Scahill & Pachler 2007, Polanczyk et al. 2007). The disorder is two to four times more common among boys than girls, though this sex difference is reduced with increasing age (Bauermeister et al. 2007, Rucklidge 2010). According to the DSM-IV-TR classification the core symptoms of ADHD are developmentally inappropriate lack of attention and/or hyperactivity, and impulsivity. Most of the symptoms are defined in observational terms as behavioural symptoms rather than emotions or perceptual symptoms. However, still it can be challenging to distinguish between the extremes of normal levels of inattention, hyperactivity and impulsivity and the levels defined as psychopathology. According to DSM-IV-TR in order to make a diagnosis, the symptoms must cause significant impairment in at least two different functional settings for at least six months, and be at a level clearly exceeding what is expected of children at the same age.

The diagnostic criteria of ADHD in the DSM-IV-TR and the research criteria of hyperkinetic disorder in the ICD-10 (World Health Organization 1993) are similarly worded. A difference is the requirement of symptoms from both the domains of inattention and hyperactivity-impulsivity symptoms in the ICD-10, which exclude the inattentive subtype according to the DSM-IV-TR from the full syndrome diagnosis in the ICD-10.

The eighteen symptom criteria of ADHD in the DSM-IV and ICD-10 hyperkinetic disorder are grouped in three domains of core symptoms: the inattentive, the hyperactive and impulsive domain. In DSM-IV-TR these domains are combined into the three subtypes of ADHD; the *combined subtype* with both inattentive and hyperactive-impulsive symptoms, the *predominantly inattentive subtype* with mainly inattentive symptoms, and the *predominantly hyperactive-impulsive subtype* with mainly hyperactive-impulsive symptoms, which is rare compared to the other subtypes (Table 1). In the ICD-10 there is no separation into subtypes, and those not meeting criteria of full syndrome hyperkinetic disorder (F90.0), may be coded as “Other hyperkinetic disorders” (F90.8). In this thesis we applied the DSM-IV-TR diagnosis of ADHD and the corresponding diagnostic criteria.

**Table 1. Diagnostic criteria of Attention-Deficit/Hyperactivity Disorder according to DSM-IV-TR Criteria for ADHD**

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**A. Either (1) or (2):**

- (1) Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:**

***Inattention***

- a. Often fails to give close attention to details or makes careless mistakes in school-work, work, or other activities
- b. Often has difficulty sustaining attention in tasks or play activities
- c. Often does not seem to listen when spoken to directly
- d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
- e. Often has difficulty organizing tasks and activities
- f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
- g. Often loses things necessary for tasks and activities (e.g. toys, school assignments, pencils, books, or tools)
- h. Is often easily distracted by extraneous stimuli
- i. Is often forgetful in daily activities

- (2) Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:**

***Hyperactivity***

- a. Often fidgets with hands or feet or squirms in seat
- b. Often leaves seat in classroom or in other situation in which remaining seated is expected
- c. Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
- d. Often has difficulty playing or engaging in leisure activities quietly
- e. Is often "on the go" or often acts as if "driven by a motor"
- f. Often talks excessively

***Impulsivity***

- g. Often blurts out answers before questions have been completed
- h. Often has difficulty awaiting turn
- i. Often interrupts or intrudes on others (e.g., butts into conversations or games)

- B. Some hyperactive-impulsive or inattentive symptoms that cause impairment were present before age 7 years.
- C. Some impairment from the symptoms is present in two or more settings (e.g. at school/work and at home).
- D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
- E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder, and are not better accounted for by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

***Based on these criteria, three subtypes of ADHD are identified:***

AD/HD, *Combined Type*: if both criteria A1 and A2 are met for the past 6 months

AD/HD, *Predominantly Inattentive Type*: if criterion A1 is met but criterion A2 is not met for the past six months

AD/HD, *Predominantly Hyperactive-Impulsive Type*: if Criterion A2 is met but Criterion A1 is not met for the past six months

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Adapted from the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000.

Some limited changes in the diagnostic criteria have been made in the new DSM-5 classification published in May, 2013. Worth noting is that the age at onset-criterion is shifted from seven up to twelve years of age, the subtypes are replaced by their modes of presentation, and an adult category of ADHD is established with requirements of less criteria than in childhood (American Psychiatric Association 2013). However, this thesis is based on the DSM-IV-TR definitions.

In general children suffering from ADHD symptoms have reduced social functioning, school performance and practical skills (Biederman et al. 2012b, Biederman et al. 2010c). These problems are linked to deficits in attention, ability to perform targeted activities, and disorganized and impulsive actions during their development (Mannuzza & Klein 2000). A group meeting both the general criteria for ADHD/hyperkinetic disorder and conduct disorder, characterized by antisocial behaviour, is considered to represent a separate syndrome rather than being part of the ADHD in childhood and youth (Biederman et al. 2008b, Klein & Mannuzza 1991, Mannuzza et al. 2008).

## 1.2.2. Adult ADHD

### *Persistence of ADHD into adulthood*

Although ADHD is considered a childhood neurodevelopmental disorder characterized by age-inappropriate levels of inattention, hyperactivity and impulsivity (Kooij et al. 2010), a significant body of research, including follow-up studies, have confirmed the persistence of ADHD symptoms into adulthood for 50-65% of the childhood patients (Biederman et al. 2012b, Biederman et al. 2012c, Barkley et al. 2002, Mannuzza et al. 1991, Kessler et al. 2005c, Polanczyk & Rohde 2007, Fayyad et al. 2007, Mannuzza et al. 2003, Lara et al. 2009, Kooij et al. 2005). Most children and adolescents with ADHD do not recover fully, and their disorder affects them further across their lifespan, leading to chronic but more covert adult ADHD symptoms in both sexes (Faraone et al. 2006a, Achenbach et al. 1995, Biederman et al. 2010b). Hyperactivity and impulsivity often decline during adolescence, while inattention tends to persist (Faraone et al. 2006a).

Some patients who are not recognized in childhood, may experience increased impairments in adolescence, and the age-at onset criterion of seven years has been considered to be too stringent (American Psychiatric Association 2013). However, most children with late onset of ADHD are younger than twelve years when meeting the diagnostic criteria (Faraone et al. 2006b). Moreover, a delayed diagnosis in adulthood does not necessarily mean a milder or sub-threshold burden of the disorder. Previously undiagnosed ADHD adults are found with as much clinically significant impairments as the childhood diagnosed (Able et al. 2007).

### *Comorbid mental disorders*

Adults with ADHD have increased risk of co-occurrence of other mental disorders, particularly drug and alcohol abuse and dependence disorders, compared to controls without ADHD (Hechtman et al. 1984, Barkley et al. 2004). Adult ADHD in many cases also goes unrecognized and may present mainly with comorbid symptoms (Barkley 2008). The prevalence of comorbid mental disorders is as high as 80% in some studies (Torgersen et al. 2006, McGough et al. 2005), and affective, anxiety and substance use disorders are most frequently reported (Halmoy et al. 2010, Kessler et al. 2006, Sobanski et al. 2007, McGough et al. 2005, Torgersen et al. 2006, Torgersen et al. 2013).

The prevalence of comorbid antisocial personality disorder (ASPD) varies in clinical samples (7% - 44%) of ADHD adults (Cumyn et al. 2009, Torgersen et al. 2006). It is evidence that some youths with conduct disorder may develop a more severe and persistent

pattern of antisocial behaviour meeting the DSM-IV criteria for ASPD (Söderström et al. 2005, Barkley & Brown 2008, Söderström et al. 2004).

Somatic health problems due to unhealthy life style such as obesity (Cortese et al. 2008), smoking (Kollins et al. 2005), drug abuse (Wilens et al. 2011a) and sleep disturbances (Gau et al. 2007) are more common among ADHD adults than in the general population. Increased prevalence of migraine and asthma are also found among ADHD patients (Fasmer et al. 2011a, Fasmer et al. 2011b).

### *Sex differences*

Unlike childhood ADHD, which is far more prevalent among boys, the sex ratios tend to be more equal in adult ADHD (Barkley et al. 2010, Faraone et al. 2006a), and some studies even find that more females than males are diagnosed with ADHD in adulthood (Groenewald et al. 2009). A review of sex differences across the lifespan, reported that females compared to males with ADHD, less frequently had been diagnosed with hyperactive-impulsive symptoms in childhood (Rucklidge 2010). Levels of ADHD symptom severity and distribution of ADHD subtypes have been found without significant differences between males and females (Grevet et al. 2006). However, in a large study (n = 536, 65% males) of sex differences (Robison et al. 2008), the authors reported that adult females were more severely affected on ADHD symptom scales than males.

Girls with ADHD are more frequently suffering from internalizing symptoms, such as anxiety and depression, than boys (Staller & Faraone 2006), and these differences seem to be maintained into adulthood (Quinn 2008, Biederman et al. 2004, Halmoy et al. 2009, Sobanski et al. 2007). In studies of adult ADHD substance abuse disorders and criminality are more prevalent among males, while affective, eating, and somatization disorders were more common among females (Rasmussen & Levander 2009, Sobanski et al. 2007). A review recommends future research to include both sexes in their samples (Rucklidge 2010) like we endeavored in our project.

## ***1.3. Symptom presentation and functional impairments in adult ADHD***

Persistent adult ADHD symptoms have serious long-term consequences (De Graaf R. et al. 2008, Kessler et al. 2005a, Able et al. 2007, Adler 2007). Levels of educational achievement



and long-term work disability are particularly relevant adult outcome measures due to the serious social, financial and personal consequences of impairments in these areas (Biederman et al. 2008).

Adolescents with ADHD have poor educational achievement compared to those who did not have ADHD as children (Barkley et al. 2006, Mannuzza et al. 1993, Hechtman et al. 1984). In a study of adult patients, all ADHD subgroups were significantly less educated and more frequently were unemployed compared with non-ADHD controls from the community (Murphy et al. 2002). Compared to controls, patients with both the combined and the inattentive subtypes of ADHD had significantly less basic education, lower proportion of graduation from college, and they were more likely to have received special education at school.

A few studies of adult ADHD have addressed whether these outcome measures vary among patients with the various childhood ADHD subtypes (Murphy et al. 2002, Sobanski et al. 2008). Sobanski et al. (2008) found that patients with all ADHD subtypes had significantly less basic education, were more frequently unemployed, and had more lifetime mental comorbidity compared to healthy controls.

Murphy et. al. (2002) reported that compared to healthy community controls, patients with both the combined and the inattentive ADHD subtypes had significantly less basic education, lower proportion of graduation from college, and they were more likely to have received special education in school.

However, a considerable literature has shown that DSM-IV childhood ADHD subtypes are unstable (Lahey et al. 2005, Nigg et al. 2010). Over time childhood hyperactive-impulsive symptoms tend to decline at a higher rate than inattentive symptoms (Faraone et al. 2006a). Based on these findings, examining the number or accumulated load of inattention and hyperactivity-impulsivity symptoms (according to the DSM-IV-TR) dimensionally, rather than by nominal subtype categories, should be more appropriate in a lifetime perspective on the ADHD syndrome (Lahey & Willcutt 2010). To our knowledge, prior to the start of our project no studies of functional outcomes in patients with adult ADHD had assessed ADHD symptoms in childhood dimensionally.

In our clinical setting, with increasing referrals of ADHD adults, it is relevant to examine the relationship between symptoms and characteristics in childhood and functioning in adult life among our patients. Few studies of adult ADHD have specifically examined childhood ADHD symptoms dimensionally and their relation to educational attainment and

work disability in adulthood. More knowledge of such associations could pave the way for tailored interventions to specific subgroups of ADHD patients, to modify and ease the burden of this disorder earlier in life. A long-time follow-up have suggested beneficial effectiveness of early interventions and medication in youths (Powers et al. 2008).

To sum up; the literature is scarce regarding the associations between childhood ADHD symptoms and characteristics, and outcomes like basic education level and work disability in previously untreated adults with ADHD. More knowledge of childhood symptoms and characteristics of those who seek treatment in adulthood can make earlier recognition possible and prepare the ground for more proper interventions in childhood.

## ***1.4. Pharmacotherapy of adult ADHD***

### **1.4.1. Previous reviews on medical treatment of adult ADHD**

Issues about use and evidence for effects of ADHD medication are currently raised in the public domain, most for children (A-magasinet 2011, Jakobsen 2013, Nyfløt 2013). Several papers on medical treatment of ADHD adults have reported efficacy of medical treatment up to twelve weeks (short-term  $\leq 12$  weeks) after initiation (Wilens et al. 2011b, Torgersen et al. 2008, Retz et al. 2011, Faraone et al. 2004). In a systematic examination and meta-analysis of 19 studies of ADHD-medications based on randomized controlled trials (RCTs) (Faraone & Glatt 2010), the authors concluded that both central-stimulant such as methylphenidate and amphetamine, as well as non-stimulant medications such as atomoxetine, were effective for treating ADHD in adults in a short-term perspective. However, stimulant medications had greater efficacy than the non-stimulants. No significant differences were found between short-acting tablets (acting under four hours) and long-acting formulations (acting over 8 hours) of stimulant medications in these short-term studies.

A PubMed search prior to our study identified no prior reviews addressing long-term medication in adults with a defined duration time above a certain time limit (Santosh et al. 2011). One review of treatment studies in general on adult ADHD (Torgersen et al. 2008) reported no trials with duration longer than 20 weeks. A literature search provided some citations that refer to long-term trials of ADHD. However, no consensus existed regarding

definition of "long term" in this field. Obviously, pharmacological interventions and studies targeting chronic, potentially life-long conditions such as ADHD need to be extended for much longer periods than for episodic disorders. Here we have decided to adopt the definition of long-term studies for treatments with duration for 24 weeks or more (Rösler et al. 2009, Rösler et al. 2010), and intermediate studies between twelve and 24 weeks.

In a paper focusing on methodological issues of stimulant medication, Hazell (2004) reviewed three psychostimulant studies of children, and argued that studies of long-term effects of stimulant medication implied specific methodological challenges such as the variable time course of the disorder, variability in adherence with treatment, and patients' decisions concerning treatment continuation. The author suggested that future research examining long-term effects of psychostimulant treatment of necessity should be naturalistic, but control for characteristics such as adherence to treatment, and variation in the course of ADHD.

To sum up, until 2009 most pharmacotherapeutic studies of adults with ADHD have been RCTs of up to twelve weeks duration. Very few studies have summarized outcomes of treatment of longer duration than 12 to 20 weeks in adult ADHD. A review examining the literature on long-term efficacy of pharmacotherapy, including a wide spectrum of outcome measures, side-effects, and effects of comorbidity, has been warranted in order to clarify the rationale for long-term medication treatment in ADHD adults.

### **1.4.2. Current pharmacotherapy**

Current Norwegian and several international therapy guidelines recommend pharmacotherapy for adults with ADHD (Norwegian Directorate of Health 2005, Canadian ADHD Resource Alliance [CADDRA] 2008, Kendall et al. 2008, Seixas et al. 2012, Atkinson & Hollis 2010, Kooij et al. 2010, Gibbins & Weiss 2007, National Steering Committee on Multidisciplinary Guideline Development 2005, National Collaborating Centre for Mental Health 2009), but recommendations concerning duration are not specified. According to guidelines, first-line medications should be psychostimulants such as methylphenidate (MPH) and amphetamines (AMP). At start of our clinical study in 2009, various formulations of methylphenidate were licensed for use in ADHD adults in Norway, but from February 1, 2011, these centralstimulant drugs were no longer approved for general use in adult patients in Norway, and prescription are as such off label.

Their mode of action is supposed to be potentiation of the amount of synaptic dopamine through blockade of the presynaptic dopamine re-uptake transporter protein. Such pharmacotherapy, although not curative, tends to effectively reduce core symptoms in 70% of treated patients in placebo-controlled efficacy studies (< 12 weeks) of adults with ADHD (Faraone & Glatt 2010). However, there is a lack of evidence for longer time efficacy of psychostimulant treatment (Meszaros et al. 2009, Torgersen et al. 2008).

Unfortunately, about 30% of adults with ADHD do not respond to central stimulants in short-term RCTs (Biederman et al. 2007), and in addition intolerable adverse effects (affecting 7 - 10%) may lead to discontinuation of therapy (Bejerot et al. 2010). Also questions about safety and risk of misuse have raised concerns about widespread use of stimulants (Wilens et al. 2008, Rappley et al. 2006, Kuehn 2009). Among non-stimulant alternatives assumed without risk of abuse, atomoxetine is a drug with clinical evidence for efficacy in adult ADHD (Adler et al. 2008, Adler et al. 2006, Adler et al. 2009a, Young et al. 2011, Durell et al. 2013, Faraone et al. 2005, Sobanski et al. 2012, Surman et al. 2010). This drug act as a selective inhibitor of the presynaptic norepinephrine transporter (Kratochvil et al. 2003), and the side-effect profile may differ somewhat from that of the stimulants (Garnock-Jones & Keating 2009).

#### *Multimodal strategies including psychosocial treatment of adult ADHD*

Current guidelines for treatment of ADHD commonly recommend multimodal strategies, which combine psychosocial treatment and ADHD medication as elements of a comprehensive treatment program (Dodson 2005). There are few studies of multimodal treatment of adults with ADHD. There is some evidence that cognitive behavioral therapy (CBT) used concurrently with stimulants improve functions parallel with symptom relief in adult ADHD patients concurrently treated with stimulants (Safren et al. 2005, Rostain & Ramsay 2006, Weiss et al. 2008). Methodological challenges of these studies include selection of comparable control groups, broad-based measures of outcome, and the possibility of type II statistical error due to small samples lacking adequate statistical power.

Most of the RCTs on ADHD medication only examine additional medical management. In open-label extension phase studies of some RCTs, however, psychosocial treatment procedures may be considered as a confounder to the observed outcomes. Due to their long-term and naturalistic design, all these studies imply some kind of supportive care in addition to medication, and it is reasonable to assume that this has some impact on patients' treatment outcome.

### *Lack of knowledge about long-term medical treatment in adults*

There are clear limitations in our knowledge about long-term effects of drug treatment for adult ADHD. Prior to our study, a number of questions concerning outcome of such treatment seem unresolved including tolerability, effects on different symptoms and mental comorbidity, issues of compliance, and effects related to outcomes like level of basic education and work disability.

We found no updated reviews which had addressed and summarized our knowledge of long-term medication in adult samples of ADHD patients. To clarify such issues it seemed warranted to conduct an updated systematical review of current knowledge on effectiveness on various measures of outcome.

Although stimulant medications are recommended as the first-line treatment in ADHD, the sparse literature on long-term drug treatment of adult ADHD had limited clinical relevance due to problems concerning sample selection, attrition and adherence, side-effects registration and other aspects of research methodology. Also, considerable variations in medication regimens both within and across nations indicated an ambiguousness of evidence. Previous reviews just recommended more observational studies to examine clinical relevance of medical treatment for adult ADHD in a longer term perspective. This status of evidence regarding medication contributed to our decision to perform a prospective naturalistic study that could consider these issues, and was a major reason for conducting study III of this thesis.

## ***1.5. Summing up of background***

An increasing number of adult patients are seeking medical treatment for persistent ADHD. The majority of patients with adult ADHD experience a chronic condition, and the treatment is therefore expected to go on for years. Therefore, the main aim of the present thesis was to study clinically relevant aspects of long-term medical treatment of adult ADHD.

We identified a lack of updated reviews of the research literature on long-term medical treatment that could clarify issues of clinical relevance for long-term pharmacotherapy with stimulants. Prior to our study, we found no consensus on the definition of long-term treatment duration. However, there was a lack of knowledge about effects of medication of ADHD adults with duration longer than 12-20 weeks. A review examining the literature on long-term

efficacy of drug treatment, including a wide spectrum of outcome measures, adverse effects, and effects of comorbidity, was relevant to clarify the evidence for long-term medication treatment in ADHD adults.

Furthermore, adult outcomes were associated with other factors than medication such as age, gender, type and levels of ADHD symptoms and comorbidity. A study of non-medicated ADHD adults could yield novel knowledge regarding these factors. To our knowledge, prior to this thesis, no study of adult ADHD had examined childhood ADHD symptoms dimensionally as predictors of functional outcomes in adulthood like attained basic education level and work disability in previously untreated adults with ADHD. More knowledge of such associations could prepare the ground for more focused studies and interventions.

Previous review articles recommended more observational studies to examine clinical relevance of medical treatment for adult ADHD in a longer term perspective. Conducting an observational study of one-year's duration in a clinical representative sample could add significantly to the literature, and be helpful to clinicians in every-day practice meeting these patients.

## **2. This thesis**

### ***2.1. Setting of the study***

The clinical study (Paper II and Paper III) was performed on the same patient sample recruited at the specialized outpatient clinic at the Division of Mental Health and Addiction, Vestfold Hospital Trust, Norway. The clinic is located in the South-Eastern part of Norway, and receives second line referrals from a region of about 250,000 adult inhabitants. Most individuals seeking general practitioners who were suspected of adult ADHD within that region were referred to the clinic, so the patient population was fairly unselected from this catchment area.

## ***2.2. Purpose and specific aims***

The overall purpose of this thesis was to study clinically relevant aspects of long-term (defined as treatment duration  $\geq 24$  weeks) medical treatment of adult ADHD, and in order to fulfill that purpose three studies were conducted:

- Study I) A literature review of studies on long-term pharmacological treatment of adults with ADHD (Paper I).
- Study II) A study of educational and occupational status as functional outcomes in previously unmedicated adult patient with ADHD referred to a specialized outpatient clinic (Paper II).
- Study III) A prospective observational study for 12 months of unmedicated adult patient with ADHD when they for the first time entered systematic medication and follow-up (Paper III).

### **2.2.1. Study I**

#### *Background*

Until 2009 we found few studies summarizing outcomes of treatment of longer duration than 12 to 20 weeks in adult ADHD. A review of long-term efficacy of pharmacotherapy, including a wide spectrum of outcome measures, side-effects, and effects of comorbidity, was suggested for further exploration.

#### *The aims*

The aims were:

- 1) To review systematically original studies of adults with ADHD, addressing efficacy and tolerability of medical treatment with at least 24 weeks duration, using either prospective or retrospective designs.
- 2) To discuss some methodological challenges encountered in long-term pharmacologic studies of ADHD.

### *The research questions*

- 1) How many RCTs and open-label prospective studies with duration 24 weeks or more were reported based on our literature base search strategy?
- 2) What are the characteristics of these studies regarding location, attrition, sample size, gender, age and comorbidity?
- 3) How is effectiveness in a long-term perspective?
- 4) How are medications tolerated, and to what degree are tolerability, adverse effects and safety reported?

## **2.2.2. Study II**

### *Background*

The research literature is limited regarding childhood ADHD symptoms and characteristics in previously untreated ADHD adults, especially concerning relationship between their childhood symptoms and characteristics, and adult outcomes of educational deficits and occupational disability, which are commonly impaired among adult ADHD patients.

### *Aims*

The aim was to examine the associations between childhood ADHD symptoms and characteristics and adult ADHD functional outcomes as educational deficits and work disability.

### *The research questions*

- 1) Whether the number of childhood ADHD symptoms, and severity of symptoms, are significantly associated with lower levels of education and long-term work disability in treatment naïve adults with ADHD?
- 2) Whether observed associations are moderated by persisting ADHD symptoms in adulthood, gender and comorbidity?



### **2.2.3. Study III**

#### *Background*

There are very few prospective studies on treatment with ADHD medications for duration of one year or more, and those identified have limitations regarding sample bias, lack of reports of comorbidities or side-effects, or have significant drop-out rates, making difficulties with drawing generalizations of treatment effectiveness to a clinical relevant target population. In addition considerable variations in guidelines for drug treatment reflect need for more observational studies on long-term medication of adult ADHD.

#### *Aims*

The aim was to prospectively examine effectiveness of stimulant and non-stimulant medication for one year of adult ADHD patients in a clinical relevant setting prospectively.

#### *The research questions*

- 1) How is the effectiveness measured by the following outcomes (ASRS, GAF, CGI-I and GSI scores) and including tolerability after one year of drug treatment of previously drug-naïve adult ADHD patients, with methylphenidate being the first-line medication?
- 2) Are outcomes moderated by age, gender, dosage, side-effects, and comorbidity?

### **2.3. Ethics**

The patient studies (II and III) were approved by The Regional Committee for Medical and Health-Related Research of South-East Norway and The Norwegian Social Science Data Services. The study protocol also was presented to the Norwegian Medicines Agency which considered Study III to be naturalistic by follow-up of patients in treatment according to the national guidelines, and therefore not in need of registration as a clinical trial. After receiving oral and written information about the study, all participants gave written informed consent before enrollment.

## **2.4. Material and methods**

### **2.4.1. Systematic search and evaluation for the review (Paper I)**

A systematic literature search was performed by assistance from the librarian at the *Norwegian Centre for Research, Education and Service* using the following electronic databases: National Library of Medicine Pubmed site, EMBASE and PsycINFO until January 2012. Published papers for the last three decades were initially searched for making use of combinations of the following search terms [Medical Subject Headings (MeSH terms) and textwords]; *ADHD*, *adult* and *stimulants*. The PubMed database got 1151 hits, EMBASE 627 hits and PsycINFO 157 hits. Additionally, in order not to be missed in the few terms initial search, we expanded the search of PubMed and EMBASE making use of multiple combinations of the search terms; *ADHD* or *Attention-Deficit Hyperactivity Disorder* (20975 hits), and added *trial*, *clinical trial*, and *long-term*, *effectiveness*, *effect*, *efficacy*, *outcome*, *outcomes*, *occupational outcome*, *work status*, *functional*, or *functions* (4580 hits).

To get medical relevant original studies on adults, we further restricted by conjugation of either of the terms; *medication*, *treatment*, *stimulants*, *psycho-stimulants*, *central-stimulants*, *methylphenidate*, *(dex)amphetamine*, or *atomoxetine* (3127 hits), and *adult* and restricted by *not child* (901 hits), *neither animal*, *nor meta-analysis* or *review articles* (549 hits). We restricted our search to papers published *in English* on human subjects aged 18 years or older at the time of evaluation in adulthood, ending up with 533 hits.

#### *Further selection and application of 'long-term treatment' definition*

Further on, by perusal of all these study abstracts, or papers in detail if the abstracts lacked relevant information, two of the authors (Fredriksen and Haavik) independently included papers meeting the a priori set requirements for inclusion of *childhood onset of DSM-IV ADHD or ICD-10*. By conferring the other authors if disagreement, we included some older studies *using the DSM-III diagnosis of ADHD* (Hechtman et al. 1984) or *the Utah Criteria* (Wender et al. 2011). Requirement of sample size was a priori set at samples with 30 subjects or more to be included to reduce bias due to small samples.

The reviewed studies included either randomized controlled trials (RCTs) with treatment duration of 24 weeks or longer, and RCTs of shorter duration with open-label

extensions of total duration of 24 weeks or longer. Due to few reported RCTs with duration more than 12 weeks (Faraone & Glatt 2010, Torgersen et al. 2008), we applied the term of *long-term treatment* defined to comprise studies of 24 weeks or more (Rösler et al. 2010).

We also included open-label studies with a prospective follow-up methodology and with reported dosage of medication with duration for one year or more in order to compare with the extension studies. We additionally agreed on that some studies excluded from the initial search procedure due to their naturalistic or retrospective design, still should be included if they either expanded the duration of treatment (several years duration) or studied functional outcomes or safety and adverse effects in long-term perspectives. The outcome measures of all studies should be broadly clinically relevant, such as ADHD symptom scores, features of mental health or comorbidity, measures of social functions, occupational status or medication tolerability.

Although based on systematic search procedures, the low number of RCTs meeting inclusion criteria in the review did not allow for standardized meta-analytic regression methodology. For description and comparison of the studies identified, we recorded characteristics of study design, sample characteristics such as mean age, gender ratio, diagnostic system and drugs used, length of follow-up, rate of responders and completers of the studies.

## **2.4.2. Subjects in the clinical study (Paper II and III)**

### *Sampling*

Referred patients aged 18 to 60 years to the specialized Outpatient Clinic were recruited consecutively, and prospectively included to the clinical studies. For inclusion, the subjects had to fulfill DSM-IV-TR criteria for ADHD, which include the presence of ADHD symptoms during both childhood and adulthood.

### *Exclusion criteria*

- 1) Comorbid mental disorder was not exclusion criteria unless assessed by a board certified psychiatrist to be in immediate need of treatment, such as current psychosis, major depression with melancholia or suicidal ideation, panic attacks with increasing

frequency, or alcohol- or substance abuse last two months. Patients with any psychiatric comorbidity considered in need of treatment should undergo at least three months adequate therapy before inclusion, and those previously treated for chronic mental disorders were included despite no remission, except for psychotic disorders, chronic substance use dependence or assessed acute suicidal risk.

- 2) Any medical contraindications for stimulant treatment such as hyperthyroidism, cardiovascular diseases or cardiac arrhythmias.
- 3) Having previously tried stimulant medication in adulthood or during the prior five years for patients 18 years of age.
- 4) An Intelligence Quotient (IQ) under 70 based on the Wechsler Adult Intelligence Scale IV (Wechsler 2008).
- 5) Assessed with clinical symptoms and behaviors consistent with a pervasive developmental disorder/autism spectrum disorder.

During the inclusion period from May 2009 to December 2010, 620 patients were referred and evaluated, and 358 (58%) were excluded since they met one or more of the exclusion criteria. Additionally 12 eligible patients declined to take part, leaving a total of 250 stimulant naïve adult patients for the clinical studies.

## **2. 5. Assessment procedures**

### **2.5.1. Psychiatric assessments**

To obtain diagnoses of mental disorders, two board-certified psychiatrists (Christian Reissig, MD and myself) examined all patients. The ADHD diagnosis was ascertained by a multistage and multisource procedure according to DSM-IV-TR criteria (Table 1) (Haavik et al. 2010, Barkley 2008, American Psychiatric Association 2000) with:

A) *The structured Diagnostic Interview for ADHD in adults, second edition (DIVA 2.0)* (Kooij & Francken 2010). We used the Norwegian version, and I had contributed to its development. To be diagnosed with ADHD, the patients must fulfil:

- 1) at least 6 out of 9 DSM-IV symptoms of inattention and/or hyperactivity/impulsivity in childhood;

- 2) currently as adults have at least 6 out of the same 9 DSM-IV symptoms for the last 6 months before the examination,
- 3) describe a chronic course from childhood to adulthood without any indication of ADHD-free periods.
- 4) We also included patients with 5 out of 9 symptom criteria for each symptom domain in adulthood if they had met full symptom criteria in childhood. These patients would be classified as ADHD NOS in DSM-IV.
- 5) The current ADHD symptoms should cause clinically significant impairment in social, educational, or occupational functioning.

Assessments by the DIVA 2.0 allowed for clinical evaluation of symptom criteria of childhood and adulthood ADHD symptoms separately.

*B) The MINI International Neuropsychiatric Interview Plus (M.I.N.I.-Plus)* was conducted in order to examine comorbid mental disorders and whether the ADHD symptoms might be better explained by another mental disorder. The M.I.N.I.-Plus is a fully structured diagnostic interview for DSM-IV mood disorders, anxiety disorders, somatoform disorders, substance use disorders, psychotic disorders, eating disorders, conduct disorder, antisocial personality disorder (ASPD), and adjustment disorder (Sheehan et al. 1998, Sheehan et al. 2002).

*C) The investigator rated Iowa Personality Disorder Screen (IPDS)* was applied to screen for personality disorders (Langbehn, 1999; Olsson, 2011). Those meeting criteria were still included in the study if the ADHD symptoms were not considered better accounted for by a personality disorder.

*D) Supplementary data* to support evidence of childhood symptoms were collected from *other informant sources* such as school records and questionnaires rated by the parents, blinded for other informants' ratings (available for 83% of the patients). *Collateral information* about current symptoms and impairment were also obtained from a close relative invited to participate during the DIVA interview with the patient. In case of discrepancy between historical data and collateral data, or collateral data from different sources, the most original information was emphasized, except for disagreement between assumed subjective judgments; when the patients' self-report had priority to parents' or spouses' report according to the DIVA instructions. *Historical data* about pedagogical assistance in primary school,

reading or arithmetic problems, grades from school reports, relevant information from other sources on childhood symptoms, such as school records and psychological-pedagogic services records, were also collected systematically.

*Physical examination* of all patients was performed by their regular physician within the past three months before the examination, in order to exclude somatic diseases. Data from medical records of previous medication were collected for each patient.

#### *Diagnostic agreement and collaboration between the two investigators*

During a pilot period at the start of the study, 21 of the examined patients had their diagnoses made independently by the two board-certified psychiatrists. The diagnoses were then compared, and the agreement was calculated with Cohen's coefficient kappa (Cohen 1988). For the ADHD DSM-IV diagnosis, the kappa coefficient was 0.77; 0.88 for the ADHD hyperactive-impulsive criteria and 0.70 for the inattention criteria. Assessments of comorbid mental disorders showed a kappa of 0.79.

### **2.5.2. Investigator-rated scales**

#### *The Global Assessment of Functioning (GAF) scale*

To evaluate overall severity of symptoms and functioning, all patients were assessed by the *Global Assessment of Functioning (GAF) scale* (Endicott et al. 1976, Hilsenroth et al. 2000, American Psychiatric Association 2000). The GAF scale which is included in the DSM-IV-TR in the section on multi-axial assessments, is an assessment tool for rating overall psychological, social and occupational functioning, and excludes physical and environmental impairment from evaluation. The presentation of the scale is accompanied by the *GAF Report decision tree* designed to guide clinicians through a methodical and comprehensive consideration of relevant aspects of a patients current symptoms and functioning to determine a patients GAF rating in a clinical setting.

The GAF was the primary outcome measure of Study III. We used the Norwegian split version discriminating symptom (GAF-S) and function (GAF-F) in order to improve reliability (Aas 2011). This version is provided with guidelines and a split decision tree, and rating of symptoms and functioning are performed separately on a scale from 1 to 100, divided into 10 equal parts providing defining characteristics, for each 10-point-interval. A

low rating reflects worse symptoms and a poorer level of functioning, whereas a high rating reflects less symptoms and a better level of functioning. The Split-GAF instrument is common in psychiatric clinical practice in Norway, and had been in use for many years at the clinic where our clinical study (Paper II and III) was conducted.

For the majority of patients this assessment was performed by the same investigator at baseline and each scheduled visit until the one-year endpoint. The two psychiatrists (Christian Reissig, MD and myself) were masked to prior assessments, and we did not take part in the psychosocial treatment. To improve our reliability, we had regular meetings, where we discussed the assessments and compared our scorings to the guidelines of GAF (Aas 2011). Prior to study start the investigators scored from patient journal records to assess agreement on inter-rater reliability, and the intraclass correlation coefficient between the assessors of GAF-S was 0.83 and of GAF-F 0.79 at baseline (n = 21).

#### *The Clinical Global Impression (CGI) scale*

The CGI scales are widely used outcome measures in several psychopharmacological studies by providing information of clinical relevance (Kooij et al. 2004, Rösler et al. 2009, Biederman et al. 2010a). The Clinical Global Impression-Improvement scale (CGI-I) is a single-item global Likert-type 7 point scale that requires the investigator to assess the patients' degree of change of the intervention from baseline (*very much improved* = 1 to *very much worse* = 7). The CGI-I scale has been found sensitive to changes of drug treatment (Lloyd et al. 2011, National Institute of Mental Health (NIMH) 2013). The *Clinical Global Impression scale* (CGI) was used as a secondary outcome measure in Study III (Guy & National Institute of Mental Health (US) 1976). In our Study III a responder was defined by dichotomized values of *much or very much improved* (CGI-I ≤ 2) versus *less improvement*.

To assess agreement between the investigators on the CGI scale, during the initial phase of the study, patients (n = 22) were prospectively evaluated independently by both investigators on the corresponding seven point CGI scale of severity (CGI-S). The intraclass correlation coefficient between the two investigators was 0.78 concerning their average measures.

### 2.5.3. Patient-rated scales

#### *The Wender Utah Rating Scale (WURS)*

To identify the severity of retrospectively assessed childhood ADHD symptoms (Study II), the patients rated the Norwegian short version of the WURS-25 (Wierzbicki 2005, Ward et al. 1993). This scale is not validated in any Norwegian sample, but has shown good psychometric properties in other languages (Retz-Junginger et al. 2003, McCann et al. 2000, Fossati et al. 2001, Caci et al. 2010). The WURS-25 items are rated on a 5-point severity scale (score range from 0-100). To simplify presentation of severity, we categorized the scaled 'WURS-25' (median = 56, mean = 56,  $SD = 17$ ) into three 'WURS-25 categories' by the lower and upper quartiles (found to be score  $< 40$  or 'low severity', and score  $\geq 70$  as 'high severity'). This corresponded well with validation studies of the scale which have set a *cut off* of score 46 or higher for great likelihood of an ADHD diagnosis, and a corresponding low likelihood of ADHD by score below 30 (Stein et al. 1995, McCann et al. 2000, Ward et al. 1993).

#### *The Adult ADHD Self-Report Scale (ASRS)*

Adult ADHD-symptoms during the last six months before baseline (Study II and III) and changes in current ADHD-symptoms from baseline to one-year follow-up (Study III) were self-assessed on the 18 item *ASRS version 1.1* (Kessler et al. 2005b). The scale can be separated in two subscales of inattentive symptoms, and hyperactive-impulsive symptoms, each of nine items respectively. We used the continuous scoring method (Kessler et al. 2005b) in order to get a wider numerical dispersion for correlation analyses. The ASRS in our sample had a Cronbach's alpha of 0.86; the inattention and hyperactivity-impulsivity subscales had alpha values of 0.73 and 0.80, respectively at baseline.

#### *The Symptom Checklist-90 Revised (SCL-90-R)*

The SCL-90-R is a broad ranged measure of self-rated mental symptoms (Derogatis & Spitz 1999). The symptoms last week before the examination are rated on a 5-point scale. The mean score of all 90 items is labeled as the *Global-Severity-Index* (GSI) (Vassend & Skrandal 1999). The SCL-90-R has been validated in a Norwegian population sample, and normative values are available (Vassend & Skrandal 1999). The GSI score was a secondary outcome measure in Study III.



## 2.5.4. Other outcome measures

### *Functional outcomes of education and work disability*

Study II contained two primary outcome measures:

- 1) *Low level of basic education* was defined as *not having completed high school*, by drop out from or interruption of the expected course of education before ending a secondary school program equivalent to high school including vocational school programs.
- 2) *Long term work disability* was defined as being out of work during the past year before entering the study, by being out of any paid work, ordinary school or studies due to ADHD-related disability.

Information about these two functional outcomes was obtained from interviews with the patients and from collateral sources. Data on education were supplemented with historical data collected from school grades and parent information, and all this information was validated during interviews with the patients. If information from various sources was contradictory, written historical and closest time data were recorded - in that order.

### *Tolerability and adverse effects*

To detect any adverse effects of treatment, *Adverse Events* (AEs) defined as ‘*any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment*’ (Graham et al. 2011, *Guideline for Industry* 2007), was recorded by free registration of complaints of the patients. In addition, we applied a quantitative measure of side-effects or tolerability by patients’ recording of symptoms by the *Canadian Attention Deficit Hyperactivity Disorder Resource Alliance* (CADDRA) ( 2011) a symptom questionnaire frequently associated with stimulant treatment; each item on an integer scale of frequency (score 0–3).

Body-weight and heart-rate, systolic and diastolic blood pressure were measured pretreatment and at each visit during treatment by whom. Electrocardiograms were performed pretreatment and at endpoint (Stiefel & Besag 2010) by patients’ GP or at the hospital, and recorded in the case report form in the study.

## 2.5.5. Procedures of treatment and monitoring (Paper III)

### *The medication algorithm*

The observational study of medication (Study III) had a prospective design. Patients were offered MPH as first-line medication combined with psychosocial treatment according to the current national treatment guidelines (Norwegian Directorate of Health 2005). Patients were assessed for symptoms, functioning and side-effects at scheduled follow-up time points: six-weeks, and three-, six- and 12-months. Standard-titration with immediate-release methylphenidate (MPH-IR) was prescribed for the first six weeks; 5 mg three times a day, stepwise increase until maximum 60 mg/day. Thereafter a flexible dose titration was applied to optimize efficacy (maximum 120 mg/day). Shift into depot-formulation/extended-release methylphenidate (MPH-ER) was offered at the three-month visit if patients reported difficulties with compliance, annoying fluctuations in effect, adrenergic side effects, or otherwise wanted to try an easier administration form. The dosage could be decreased at any time during follow-up depending on tolerability.

If methylphenidate was not tolerated or was ineffective, alternative medications were short-acting dextroamphetamine (dAMP) or atomoxetine (ATX). The dAMP was titrated until maximum 50 mg/day, and dose of ATX began with 25 mg/day for seven days, and was followed by 40 mg until a maximum of 120 mg. Patients could use additional medication in the treatment of any comorbid mental disorder that was indicated, but such medication should not have been initiated within last three months before, and first three months after the baseline assessment. If such other drug treatment was initiated more recently by the patient's psychiatrist or GP, the start of ADHD medication was postponed accordingly.

### *Blood sampling and adherence*

In a pilot study we performed non-announced blood-sampling and examined methylphenidate plasma-concentration from 12 consecutive patients, who claimed to have taken their medication 2-3 hours earlier that day. In all of these patients the plasma levels of ritalinic-acid were compatible with intake of therapeutic amounts of methylphenidate in all cases (MPH mean daily-dose 47.0 mg,  $SD = 16.5$ ), plasma-concentration mean 1962 nmol/l ( $SD = 742$ , range 798–3889).

Adherence to medication was assessed indirectly for all patients by interviews and accounts of prescriptions; taking prescribed less than 70% of doses for the days since the last

visit was considered non-compliance according to procedures applied in studies of adherence (Bosley et al. 1995, Eatock & Baker 2007). To ensure abstinence from narcotics required to maintain ADHD-medication, health care staff supervised urinary screenings of patients reporting any substance use last year, and the assay was performed by liquid chromatography and mass spectrometry.

## **2.6. Statistical analysis**

### **2.6.1. General analyses**

Due to the low number of RCTs meeting the inclusion criteria in Paper I, the review did not suit for standardized meta-analytic regression methodology, and therefore the paper basically was performed as a systematic descriptive review.

All statistical analyses in Study II and III were carried out by The PASW Statistics, version 17.0 for PC (2009). The data were initially analyzed by descriptive methods. On the group level, categorical variables were analyzed using the chi-square test, and stratified in order to explore for sex effects (Grevet et al. 2006). Differences in the continuous outcomes were analyzed with t-tests when the assumption of normal distribution was met, and otherwise with non-parametric tests. The level of significance was a priori set at  $p < 0.01$  because of the multiple tests performed. All tests were two sided. The continuous scores of the WURS-25 and ASRS inattention subscales were categorized into *low*, *moderate* and *high* levels by the quartiles in order to get a more clinically relevant representation.

In Study II logistic regression analyses with ‘not completed high school’ as the dependent variable were adjusted for *gender*, but not *age* since predictors should antecede the predicted factor. The work status analyses were conducted adjusted for both age and gender. The specified independent variables were entered into logistic regression models initially unadjusted one at a time, and finally adjusted by entering age and gender together. Corresponding odds ratios (ORs) and their 95% confidence intervals (95% CI) were estimated as measures of strength of associations, and the level of two-tailed significance was set at  $p < 0.05$ .

In Study III power analysis determined the sample size with the assumption that about 200 patients would complete at 12-month. Patients continuing *on-medication* were compared to those *off-medication* in a visit-wise analysis, and tests for independent groups were used to assess the differences between groups at follow-up. Changes in outcome variables from baseline to endpoint in individuals were analyzed using paired sample tests.

## 2.6.2. Longitudinal mixed model analyses

These analyses were performed under the supervision of Ole Klungsøyr, PhD, medical statistician at the Institute for Clinical Medicine, University of Oslo. Longitudinal analyses by linear mixed models (LMM) (McCulloch 2006) were planned to assess change over time in the following outcomes: ASRSv.1.1, GAF-S, GAF-F and GSI at scheduled follow-up visits. Several baseline variables considered to be potential confounders for the association between treatment and outcome were adjusted for: *gender*, *age* at inclusion, indicators for *depression*, *bipolar or anxiety disorder*, *substance and alcohol use disorder and antisocial personality disorder*. Model selection was based on maximum likelihood (and restricted maximum likelihood) and non-significant covariates were excluded. The time courses of the outcomes were modeled with two piecewise linear splines, prior and following time point  $t^*$ , where  $t^*$  was 6 weeks for ASRS and 26 weeks for GAF-S, GAF-F and GSI.

To assess a dose-response effect of treatment a cumulative dose variable was constructed (*CumD*). Side effects (*SideEff*) were measured (CADDRA) and served as a time-varying covariate. A cumulative side-effect variable was also constructed (*CumSE*). Higher equivalent dose of medication was associated with higher *SideEff*, and higher *SideEff* predicted less medication in the next period and also more loss to follow-up. Thus, *SideEff* plays a role, both as a potential time-varying confounder and a source for selection bias (from loss to follow-up). In the present model, *CumSE* is adjusted for to reduce the selection bias, and to give a conservative estimate of the treatment effect (adjustment reduced the treatment effect).

The following equation describes the model (with adjustment for one baseline confounder):

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i}) \times st_{1j} + (\beta_2 + b_{2i}) \times st_{2j} + \beta_3 CumD_{ij} + \beta_4 CumSE_{ij} + \beta_5 X_{1i} + e_{ij} \quad (1)$$

where  $Y_{ij}$  is outcome for person  $i = 1, \dots, 250$  at time point  $j = 1, \dots, 5$ ,  $e_{ij}$  is the error-term,  $\beta_0, \beta_1 \dots$  are the fixed effects (population averages),  $b_{0i}, b_{1i} \dots$  are the individual specific random intercepts and slopes before and after  $t^*$ , the two spline time-scales are  $st_{1j} = \min(time_j, t^*)$  and  $st_{2j} = \max(0, time_j - t^*)$  and the two cumulative covariates are given by

$$CumD_{ij} = \sum_{k=0}^j Dose_{ik}, \quad CumSE_{ij} = \sum_{k=0}^j SideEff_{ik} \quad (2)$$

### 3. Results

#### 3.1. Review of long-term efficacy and safety of medical treatment (Paper I)

1) *How many RCTs and open label prospective studies with duration 24 weeks or more were reported based on our search strategy?*

We identified five papers of four separate RCTs with duration  $\geq 24$  weeks (Rösler et al. 2009, Rösler et al. 2010, Biederman et al. 2010a, Adler et al. 2009a, Young et al. 2011); two of the studies were from the same trial (Rösler et al. 2009, Rösler et al. 2010) (Table 2). All these studies observed significant differences in symptom reduction favoring active medication versus placebo. However, in general these trials provided limited information about changes in functional outcomes. Additionally, 11 initially short-term RCTs were pursued by an open-label extension of the observation period for a total duration of  $\geq 24$  weeks (Ginsberg & Lindefors 2012, Marchant et al. 2010, Wender et al. 2011, Adler et al. 2009b, Biederman et al. 2005, Weisler et al. 2005, Ginsberg et al. 2011, Adler et al. 2005, Adler et al. 2008, Buitelaar et al. 2011, Marchant et al. 2011) (Table 3). In eight studies medication was methylphenidate, in four atomoxetine and in two amphetamine.

We also included 18 studies with naturalistic or cross-sectional design reporting broader measures of outcomes related to treatment, tolerability or safety (Hechtman et al. 1984, Bejerot et al. 2010, Weiss et al. 2010, Adler et al. 2011, Powell et al. 2011, Powers et al. 2008, Biederman et al. 2009, Halmoy et al. 2009, Gjervan et al. 2012a, Barkley et al. 2003,

Faraone et al. 2007, Biederman et al. 2008a, Klein & Mannuzza 1988, Kramer et al. 2000, Biederman et al. 2010c, Cooper et al. 2011, Habel et al. 2011, Schelleman et al. 2012).

*2) What are the characteristics of these studies regarding location, attrition, sample size, gender, age and comorbidity?*

Half of the RCTs, and the majority of the extension studies were performed in United States, and commonly had frequent drop-outs (> 30%), had samples of both sexes, and mean age ranged about 35 – 40 years. Comorbid mental disorders were exclusion criteria in most of the studies. In eight studies medication was methylphenidate, in five atomoxetine and in two amphetamine.

*3) How is effectiveness in a long-term perspective?*

The four RCTs showed significant differences in symptom reduction favoring medication, and these differences were maintained through the follow-up periods (Table 2).

In the RCTs with open label extension the efficacy demonstrated during the acute placebo-controlled phase, was either maintained or further improved during the extended follow-up period (Table 3).

Some naturalistic studies reported a positive correlation between treatment with central stimulants and a positive educational development (Hechtman et al. 1984, Powers et al. 2008, Biederman et al. 2009). Notably, treatment with stimulants in childhood was found to be a significant predictor for being employed in adulthood, and older age at treatment initiation was associated with poorer occupational outcomes (Halmoy et al. 2009, Gjervan et al. 2012a). Regarding risk of developing substance use disorders (SUDs), several naturalistic studies found no link between prior pharmacotherapy for ADHD and subsequent SUDs (Faraone et al. 2007, Barkley et al. 2003, Biederman et al. 2008).

*4) How are medications tolerated, and to what degree are tolerability, adverse effects and safety reported?*

In all the placebo controlled and extension studies, the medication was well tolerated of most patients, and most adverse effects occurred during initial titration phase. Decreased appetite, nausea, palpitations, mucosal dryness, and dizziness were the most frequent side effects

(frequency between 10-40%). Some epidemiologic studies of adverse effects on large samples of people using central stimulants did not report any significant associations with any increased risk for serious cardiovascular events compared to none-users (Cooper et al. 2011, Habel et al. 2011, Schelleman et al. 2012).

Data in the following tables (Table 2 and 3) are adapted from data published in Paper I and displays characteristics from the controlled studies which were included in this study.

Table 2. Randomized double blinded placebo-controlled trials with duration ≥ 24 weeks				
Authors	Medication	Measures	Results	
Rösler et al. (2009)	Methylphenidate extended release (MPH ER) and MPH immediate release (MPH IR)	<i>Primary outcome:</i> Response: 30% reduction WRAADDS <sup>a</sup> score	61% responders receiving MPH ER versus 42% responders in the placebo group. Completers 69%. Premature termination (31%); 24% MPH ER versus 43% placebo. Number needed to treat statistics (NNT) was 6	
Rösler et al. (2010)	#Same trial above	<i>Primary outcome:</i> WRAADDS; reduction of EDS (Emotional Dysregulation Scale, observer rated, 10 items from)	MPH-ER superior to placebo reducing emotional symptoms on EDS and ELS, significant from week 5, Cohen's d effect size 0.3	
Biederman et al. (2010)	Osmotic Release Oral System MPH (OROS MPH)	<i>Primary outcome:</i> CGI- improvement scale (CGI-I): Much or very much approved (CGI-I ≤ 2), and AISRS <sup>c</sup> reduction > 30%	Phase 1; OROS MPH group 62% responders, versus placebo responders 37%. Phase 2; Rate of completers did not differ, OROS MPH responders were more likely to drop out of adverse effects, placebo responders by loss of effect. Phase 3; OROS MPH responders who completed phase 2, randomized for a 4-week, placebo controlled discontinuation: The time by treatment interaction for AISRS was statistically significant. Relapse-rate did not differ (18% in both groups)	
Adler et al. (2009)	Atomoxetine (ATX)	<i>Primary outcome:</i> AISRS reduction from baseline	Mean AISRS total scores for ATX decreased from 38.2 at baseline to 21.4 at the 6-month end point. Placebo from 38.6 to 25.8. Completers: (38%) patients randomized to ATX, (45%) patients randomized to placebo completed the study	
Young et al. (2011)	ATX	<i>Primary outcome:</i> CAARS-Inv:SV, Response: 25% decrease on CAARS-Inv:SV	CAARS-Inv:SV Total score reduction was greater with ATX over placebo at 12 weeks (-14.3 vs -10.1) and 24 weeks (-16.4 vs -8.6; effect size, 0.6). Response: greater for ATX (68%) than placebo (42%) at 24 weeks NNT was 4	
a. The Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS)				
b. The Conners' Adult Attention Deficit/Hyperactivity Disorder (ADHD) Rating Scales (CAARS) – Observer: Short Version (CAARS-O:SV), CAARS-Self report (CAARS-S), CAARS-Investigator Rated: Screening Version (CAARS-Inv:SV), CAARS Rating Scale–Self-Report: Long. Version (CAARS–S:L)				
c. The the Adult ADHD Investigator Symptom Rating Scale (AISRS)				



Table 3. Studies with short-term RCT and open-label extension phase				
Authors	Medication	Measures	Results	
Ginsberg & Lindefors (2012)	Osmotic Release Oral System Methylphenidate (OROS MPH)	Change in CAARS-O:SV <sup>a</sup> Adult ADHD Self-Report Scale (ASRS) <sup>b</sup> Clinical Global Impression of Severity (CGI-S) Global Assessment of Functioning (GAF)	Improved ADHD symptoms (Cohen's d effect size, 2.2). Response (30% decrease of CAARS-O:SV at week 5); 87% responded to OROS MPH compared with 0% for placebo; ASRS, CGI and GAF improved during open-label extension. All completed. NNT was 1.1	
Buitelaar et al. (2011)	OROS MPH	CAARS:O-SV <sup>a</sup> band CGI-S CAARS-SSDS Sheehan Disability Scale	Mean CAARS:O-SV score decreased 1.9 from baseline. Small statistically significant improvements observed for CAARS-S, CGI-S and SDS. Completers : 63%	
Marchant et al. (2010)	OROS MPH,	WRAADDS <sup>c</sup> defined sub-groups: (ADHD) alone, emotional dys-regulation (ADHD+ED), and plus oppositional defiant disorder (ODD). ADHD-Rating Scale (ADHD-RS) <sup>d</sup> . Personality disorder PD)	Maintained improvement on all 3 WRAADDS-defined dimensions; attention+ disorganization by 61%, hyperactivity-impulsivity by 60%, emotional dysregulation 66% for all subgroups. ADHD+ED+ODD group showed most long-term improvement on social maladjustment. PD patients were less likely to complete or show improvement. Completers of open-label phase: 44%	
Wender et al. (2011)	Immediate release MPH (IR MPH)	Respos: 50% reduction of observer rated WRAADDS. Clinical Global Impression of Improvement (CGI-I) Global Assessment of Functioning (GAF)	In the double blind trial more subjects in IR-MPH group responded (74%) versus placebo (21%). During open-label trial, symptom severity decreased 80% from baseline, WSAS decreased > 50% in all subscales indicating improvement. Average GAF improved significantly. Completers: 73%	
Adler et al. (2009)	Dex-MPH extended release (dMPH ER)	ADHD-RS <sup>d</sup> Proportion of responders on CGI-I	60% completed. Mean improvement on ADHD-RS (-10.2) switching from placebo to d-MPH-ER, and (-8.4) for they who maintained on d-MPH-ER. Respective CGI-I responder rates were 95.0% and 95.1%	
Biederman et al. (2005)	Mixed amphetamine salts extended release (MAS XR)	ADHD-RS-IV <sup>d</sup> Safety assessments (adverse events, laboratory assessments, and monitoring of vital signs)	ADHD symptoms significantly improved from baseline in mean ADHD-RS-IV total scores (-7.2 unit points); this was sustained for up to 24 months.	
Weisler et	MAS XR	Resting sitting diastolic blood pressure (BP) and	Mean change in diastolic BP (1.3 mmHg), systolic BP (2.3 mmHg) and pulse	

al. (2005)		systolic BP, and pulse at baseline, and weekly, then monthly. ECG	(2.1bpm) were small. On ECG, QTc (corrected by Bazett's formula) increased 7.2 msec observed at 24 months
Ginsberg et al. (2011)	Lisdex-amphetamine-dimesylate (LDX)	<i>Response</i> : ADHD RS-IV <sup>d</sup> (ADHD-RS-IV) decrease 30% from baseline <i>Remission</i> : ADHD-RS-IV score $\leq 18$ CGI-S; Post hoc stratification	Clinical response according to stratification of severity (CGI-S = 4, 5, and $\geq 6$ , respectively): 79%, 84%, and 88%. Symptomatic remission criteria by 64%, 65%, and 72%. Increased mean change of ADHD symptoms with greater baseline symptom severity (5,6). Completers: 55%
Adler et al. (2005)	Atomoxetine (ATX)	CAARS-Inv:SV total ADHD symptom score.	Significant improvement on ATX, mean CAARS-Inv:SV total ADHD symptom scores decreasing 33.2% from 29.2 (baseline of open-label therapy) to 19.5 (endpoint of open-label therapy)
Adler et al. (2008)	ATX	Change of CAARS-Inv:SV <sup>b</sup> Total ADHD Symptom scores Sheehan Disability Scale	CAARS-Inv:SV Total ADHD Symptom scores decreased 30.2% ( $p < 0.001$ ) during treatment. Significant decreases for the secondary efficacy measures, including the Sheehan Disability Scale Total score, improved 25.3%. Completers: 18%
Marchant et al. (2011)	ATX	WRAADDS, CAARS-Inv:SV, Response CGI-S score $\leq 3$ last visit	Previously responders from the RCT phase achieved maximum response after 8 weeks of open-label medication, but others continued to improve for 36 weeks. During open-label treatment 39% percent of ATX double-blind non-responders became responders. Completers: 18%
a. The Conners' Adult Attention Deficit/Hyperactivity Disorder (ADHD) Rating Scales (CAARS-S), CAARS-Investigator Rated:Screening Version (CAARS-Inv:SV), CAARS Rating Scale-Self-Report: Long. Version (CAARS-S:L)			
b. The Adult ADHD Self-Report Scale version 1.1 (ASRSv1.1)			
c. The Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS)			
d. The ADHD Rating Scale IV (ADHD-RS-IV)			

### **3.2. Educational failure and long-term work disability (Paper II)**

*1) Whether the number of childhood ADHD symptoms and severity of symptoms are significantly associated with lower levels of education and long-term work disability in treatment naïve adults with ADHD?*

High levels of ADHD symptom severity in childhood measured by WURS 25 (high severity score  $\geq 70$ ) were significantly related to shorter duration of basic education and dropping out of high school (odds ratio = 3.0). Also, higher numbers of hyperactive-impulsive symptoms in childhood were significantly related to interrupted schooling (by each symptom criterion odds ratio = 1.2). Work status was hardly related to differences in ADHD characteristics in childhood.

*2) Whether observed associations are moderated by persisting ADHD symptoms in adulthood, gender and comorbidity?*

Fifty-six percent of the sample had not completed secondary school equivalent to high school, and no significant difference between the sexes was observed. However, statistically significant more males (53%) than females (36%) were in paid work or attending ordinary studies ( $p = 0,009$ ), and more females (58%) than males (41%) had disability or rehabilitation pension ( $p = 0.005$ ). After adjusting for age and gender, persisting high levels of ADHD inattention-symptoms in adulthood (odds ratio = 2.5), and number of adult comorbid disorders (odds ratio = 1.6) were all significantly associated with long-term work disability.

### **3.3. Effectiveness of one-year medical treatment (Paper III)**

*1) How is the effectiveness including tolerability after one year of drug treatment of previously drug-naïve adult ADHD patients, with methylphenidate being the first-line medication?*

Among the 250 patients who started with medication, 232 (93%) completed examination at the 12- month follow-up, and 70% ( $n = 163$ ) remained on medication, mostly on methylphenidate (80%). Those patients continued on any ADHD medication had a

statistically significant improvement of primary and secondary outcome measures at one year follow-up compared to their non-medicated baseline. Those who discontinued medication, also experienced statistically significant improvements, but to a lesser degree (Figure 1).

Comparing primary outcomes of those on medication to those off at one-year follow up, a significantly greater improvements in global symptoms and functions by the GAF-S and GAF-F (median 20% versus 2%, and  $p < 0.001$ , and 18% versus 6%,  $p < 0.001$ , respectively) were found.

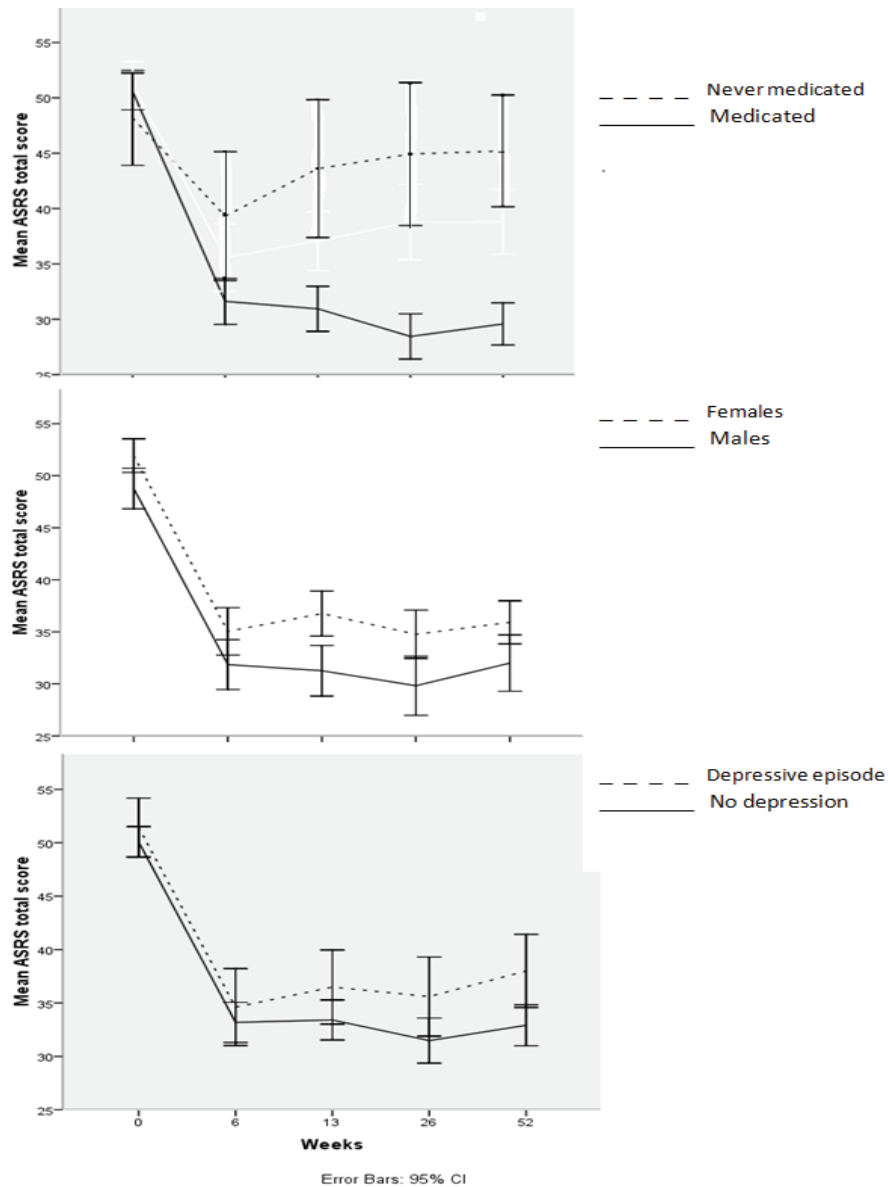
Compared with patients who discontinued medication, those still on medication at 12-month follow-up had greater proportions of reductions in ASRS-scores (median 39%, versus 13%,  $p < 0.001$ ), and significant and corresponding reductions in both adult inattention and hyperactivity/impulsivity symptoms were observed (median 39%, versus 13%,  $p < 0.001$ , and median 39%, versus 13%,  $p < 0.001$  respectively). Corresponding findings were reported on secondary outcomes, such as mental distress by the GSI measure (SCL-90-R mean values, 46% versus 23%,  $p < 0.007$ ), and higher responder rate of the investigator rated CGI-I by a priori response definition of the values of *much or very much improved* ( $\text{CGI-I} \leq 2$ ) (median 87% versus 3%,  $p < 0.001$ )

Frequencies of adverse effects were generally low. Of the 69 patients (28%, 69/250) who had discontinued medical treatment before 12- month follow-up, 31 (12%) terminated due to side-effects. Nine had to stop medication because of elevated blood pressure, and notably, all of these had a borderline high level at baseline. No serious adverse effects occurred, and there was no significant prolongation in electrocardiographical QT time.

## *2) Are outcomes moderated by age, gender, dosage, adverse effects, or comorbidity?*

Longitudinal analyses showed significant associations between sustained improvement and being on medication at 12 month follow-up (Figure 1). Conversely, mental comorbidity and adverse effects were related to significantly lower effectiveness and more frequent termination of medication before 12 month follow-up. With the applied titration algorithm, higher dosage of medication over time (cumulative dose) was associated with greater improvement on the primary outcome measures ( $p < 0.001$ ).

**Figure 1. Longitudinal ADHD symptom outcome stratified by medication, gender and comorbid depression**



Data from Paper III, outcome of mean Adult ADHD Self-Report Scale (ASRS) total score paneled by group of adherence to medication, by gender and by depressive episode last year before admission. The *never-medicated* group (n=20): patients discontinued MPH-treatment within first six-week follow-up, and never started up with any ADHD-medication. The *medicated* group (n=140): patients used ADHD-medication at every follow-up visit.

## 4. Discussion

### 4.1. *Methodological issues*

#### 4.1.1 **Methods of the systematic review (Paper I)**

The review was primarily planned to be performed by a systematic search procedure, to include all relevant RCT studies or prospective controlled studies of ADHD medication of adult patients with long-term ( $\geq 24$  weeks) duration. We soon realized that very few RCTs had been conducted, and that a quantitative meta-analysis methodically was not suitable. However, data to compare number needed to treat (NNT) could be estimated for some of the studies.

Our sampling procedure of the RCTs and open label extension studies from RCTs included a systematically retrieved sample within the applied dates and chosen bibliometric terms for the search. The initial broad search in several large databases and further systematical restricting procedures, intended to ensure that all relevant papers were included. By use of synonyms or overlapping words as MeSH terms, it is less likely that we have missed any relevant studies from sample of the study. However, regarding further selection of open-label prospective studies without an initial controlled phase, the risk for missing studies is more present due to MeSH terms in use can be more varied. We did not perform search manually based on the reference lists of papers already identified.

The retrospective, or large epidemiological studies that we also included were not result of the systematic selection procedures, as they were added to enlighten and discuss some clinical important issues not examined in the controlled and prospective studies. This part of the Paper I is therefore unsystematic retrieved, though, all these studies too, were included in the initial broad search, before any restrictions were made. The authors' professional knowledge of the literature of the field contributed partially to this subsequent selection.

Two of the authors perused all the abstracts from the initial electronic search, and excluded papers not meeting the inclusion criteria (see section 2.4.1). For the sake of reliability they compared their of lists of included papers, and discussed disagreements, and the other authors were consulted in case of disagreements.

#### **4.1.2 Methods of the clinical studies (Paper II and III)**

##### *Design*

Study II and III were performed on the same patient sample, but had different designs. Study II, with the aim to investigate associations between adult functional outcomes, and childhood ADHD symptoms, had to examine retrospectively childhood characteristics, and in that way to rely on the memory of the informants. Most studies on adult ADHD in the literature are cross-sectional or retrospective, and few studies have compared adult impairment to childhood symptoms or characteristics. The retrospective design does not allow us to draw general inferences about the consequences of childhood ADHD symptomatology for function in adulthood. Our prospective and consecutive recruitment procedure precluded selection bias of patients. Recall biases of the patients were reduced by conferring their information with historical data and collateral data sources.

Study III was conducted as a clinical cohort prospective observational study with open label design without control group. However, unlike pure naturalistic designs, some standardization was performed to facilitate examinations by comparisons of time and group-related factors. Standardization implied that all patients started with the same medication, applied the same titration procedure for the first six weeks, and all patients were followed up according to a priori scheduled visits by repeated use of measures that were both investigator-rated and self-rated. Similar standardizing of the assessment and treatment implemented in the study design are also described in two other observational studies (Adler et al. 2011, Weiss et al. 2010) to reduce confounding variance and simplify interpretation of effectiveness.

According to our design longitudinal mixed model regression analyses were required to explore models of associated and confounding factors related to our outcome variables. Deciding upon one-year as the final follow-up provided a common end-point for measures of individual changes from pre-treatment, and between groups by different characteristics. However, the uncontrolled open-label design has clear methodological limitations like inferences of causality cannot be drawn. A controlled design with placebo group would eliminate confounding of the main symptomatic relief or functional improvement outcomes on a specific treatment regime, since confounders would be randomly distributed between the actively treated and the placebo patients. Conducting a long-term RCT however, would be too demanding with regards to expenses of masking patients and investigators at repeated

measurements over a long time period, and not at least it would challenge ethical issues of being exposed to long-term placebo with potential lack of efficacy.

#### *Patient sample and referral practice*

We conducted a simple power analysis assuming between 50% and 70% patients completing one year treatment based on reports from a national project on trying out psychostimulants for adults (Aanonsen et al. 2005). We considered about 150 patients to be sufficient for most analyses between two groups ( $n = 75 * 2$ ), since with  $p < 0.05$ , and statistical power (beta) of 0.80, effect sizes of  $\geq 0.30$  would represent clinical significant differences (Cohen 1988).

To end up with about  $n = 150$  patients completing the effectiveness study (Paper III), we had to include about 250 patients at baseline due to the expected attrition of 40% of the patients during the one-year duration of the study.

However, more patients than expected completed, improving the statistical power of Study III. The sizes of the samples of studies II and III are large compared to corresponding studies in the literature. To the best of our knowledge Study III comprised the largest single-site clinical cohort prospective study on medication-naïve adults, evaluating long-term effectiveness of ADHD medication.

These samples included adults consecutively referred by their GPs or primary referral outpatient psychiatric clinics. Most likely more than 90% of all help-seeking adults suspected with ADHD from our catchment area are referred to our specialized outpatient service, since diagnosis and initiation of ADHD medication was allocated to this service by the regional health trust. Due to this recruitment procedure the patients can be considered as without selection bias from our catchment area.

The reason for referral was relate to recognition of some kind of impairment or suffering from ADHD-like symptoms or being identified with behavioral problems known to be associated with ADHD. In that way referrals would reflect knowledge about ADHD in the general population, and among the GPs of the catchment area, when it comes to patients suffering from ADHD alone. Patients with conspicuous mental comorbidities were expected to be referred from general psychiatric outclinics. In our sample about half of the patients were referred from the specialist health care. Concerning frequency of comorbidities, this could lead to a selection bias due to those with comorbid mental disorders may more likely be referred like *Berkson's Fallacy* (Berkson 1946).



### *Diagnosis and measures of symptoms*

The reliability and validity of the adult ADHD diagnoses were addressed by the two board certified psychiatrists who both were quite experienced with the ADHD patient group, and who had worked together at the outpatient clinic for some time before the study start. They also met regularly during the study to discuss diagnostics and their approaching of the multistage and multisource procedure described in the above section (2.5.1). In a pilot study prior to initiation of the inclusion period, they achieved satisfactory diagnostic agreement indicating satisfactory reliability of their independent diagnostics.

Explaining-validity and nature of psychiatric diagnosis in general (Phillips et al. 2012), and the ADHD diagnosis in particular (Asherson et al. 2010, Moncrieff & Timimi 2010, Kooij et al. 2005, Kooij et al. 2010), is considered beyond the scope of this thesis. Our diagnostic procedures to achieve optimal diagnostic agreement between the investigators correspond to that recommended elsewhere for clinical studies of adult ADHD (Barkley 2008, Haavik et al. 2010, Kooij & Francken 2010). An achieved overall Cohen's kappa coefficient ( $\kappa$ ) about 0.8 of diagnosis is considered a more robust measure than simple 80 percent agreement calculation, since it takes into account the agreement occurring merely by chance. Some quarters have expressed criticism over  $\kappa$ 's tendency to take the observed categories' frequencies as given, which may lead to underestimating agreement for a category that is commonly used, and therefore  $\kappa$  may be a conservative measure of reliability (Strijbos et al. 2006).

Number of diagnostic symptom criteria from the *Diagnostic Interview for ADHD in adults, second edition* (DIVA 2.0) were counted and correlated with the outcome measures in Study II. In this way we got an investigator-rated numerical measure of ADHD symptom dimensions both in the childhood and adulthood. However, this evaluation is also retrospectively based with regards to the childhood ADHD criteria, and they may be biased by difficulties of both patients and relatives concerning recall of childhood symptoms and dysfunction.

Several psychometric instruments were applied. We chose global assessment scales for the investigator-rated outcomes in Study III. This was partly due to lack of an ADHD investigator-based rating scales in Norwegian at that time, but also due to limited resources available of the psychiatrists to perform such interviews at repeated sessions.

The Global Assessment of Functioning scales (split GAF) were chosen over the Clinical Global Impressions-Improvement scale (CGI-I) as primary outcome, since we

achieved somewhat greater inter-rater-reliability (0.83 versus 0.78) on the continuous scores, and GAF also indicated functional changes. However, as a secondary outcome in our study, the CGI-I was used for defining the responder rate as commonly done in psychopharmacological studies (Biederman et al. 2010a, Rösler et al. 2009).

Patient-rated scales were used both for assessment of childhood ADHD symptoms severity (WURS 25), and for current ADHD symptoms (ASRSv1.1) (Section 2.5.3). These scales were not used for diagnostic purposes, but for continuous rating of the levels of ADHD symptoms used for correlations and regression analyses. There are methodological issues inherent in self-ratings concerning variance due to subjective attribution and references. In Study II, level of childhood ADHD severity measured by the WURS 25 correlated with levels of self-rated current ADHD symptoms by the ASRS (Spearman's  $\rho$  0.51,  $p < 0.001$ ), possibly partially due to attribution and recall. However, in Study III, the assessed changes in the ASRS by repeated measures were expected to be less influenced by such biases, assumed this kind of bias was most expressed by individual variance of baseline levels.

### *Treatment issues*

In Study III all patients were subjected to the same treatment algorithm first six weeks. Thereafter individual titration and shift of medications were possible, though only if methylphenidate was considered to be not tolerated or ineffective. In this way, all the patients tried methylphenidate initially, and a selected group of patients additionally tried one or more of the other drugs; amphetamine or atomoxetine. Hence, we cannot compare the effectiveness of these drugs, since these selected patients assigned to second choice drugs presumably represent different characteristics of tolerability and responder capability than those continuing on methylphenidate. Also decisions to shift drug to atomoxetine or amphetamine was taken on clinical judgment emphasizing various characteristics; implying Non-random assignment of second medication.

Though, it was not the aim of the study to compare effectiveness between ADHD drugs, we rather wanted to explore effectiveness of a current clinical applied ADHD drug treatment regime; starting up with methylphenidate, and made changes of medication under certain predefined conditions such as lack of efficacy or intolerable adverse effects. It may be argued that this medication algorithm makes it difficult to interpret outcomes of single drugs. If one can change dosages, or shift medication along the course, what treatment represents the final outcome? To simplify analysis, we presented stratified courses by different groups of

patients in Paper III. I should also underline that associations found in the longitudinal analyses cannot be interpreted as causal mechanisms. With our uncontrolled design, we are limited to discussions of estimates of possible causal associations and probable confounding factors.

## **4.2. Discussion of the main findings**

### **4.2.1. The review of long-term medication studies (Paper I)**

In the following section of discussion, our main findings of the research questions are discussed in light of results from other relevant studies, emphasizing how our findings may add to the literature, and with discussion of notable strengths and limitations of these results.

*1) How many RCTs and open label prospective studies with duration 24 weeks or more were reported based on our search strategy?*

Long-term have been defined in our review, but search was performed initially by the key words without specifying time restriction of these terms. We identified only four separate RCTs with duration  $\geq 24$  weeks, and additionally 10 initially short-term RCTs which were pursued by an open-label extension of the observation period for a total duration of  $\geq 24$  weeks. In eight studies medication was methylphenidate, in four atomoxetine and in two amphetamine. Other drugs for ADHD are not found with such studies in that long term perspective. We also included 18 treatment studies with naturalistic or cross-sectional design reporting other outcome measures or safety.

At the time of the planning of this study, few reviews had reviewed long-term treatment studies (Faraone & Glatt 2010), probably due to the very limited number of such studies performed. The small amount of long-term RCTs found, may be explained by the ethical and financial obstacles with conducting longer randomized placebo controlled studies. Current stimulant drugs of treatment have been in use for many years, and given the established efficacy and safety profile in short-term studies of ADHD medications, it would be hard to assume that ethical committees would approve the use of placebo for longer terms. However this would be the gold standard design to prove efficacy.

To our knowledge this study of literature is unique in addressing questions of long-term efficacy of ADHD drug treatment of adult patients, and performing an updated systematic review of studies on effectiveness. Most of the articles retrieved were open-label treatment studies, but some of the naturalistic studies prospectively followed adolescents over many years and including young adulthood (Biederman et al. 2009, Powell et al. 2011, Biederman et al. 2008a).

Strength and limitations concerning collecting the articles: Although the literature search was carried out using several large electronic databases and by overlapping MeSH terms and text words, we cannot be sure that all relevant open label studies were identified. It is a limitation that we did not perform search manually on the reference lists of the papers found. However, it is unlikely that we have missed any published long-term RCT study, since they are few, and RCT or trial then would be obligate MeSH terms.

The question may be raised whether performed studies of showing lack of efficacy of drug treatment have been published. All of the RCTs and RCT extension studies with commercial sponsors in the review (Table 2 and 3), are recently published after the requirements of mandatory registration of clinical trials became obligatory in 2005 (Zarin et al. 2005). However, it is hard to make any reasonable estimate of proportion of unpublished negative studies on this field, and we have not performed any search in the clinical trial registry to tentatively address this question. In contrast to the RCTs, the naturalistic studies do not have mandatory registration, and may such not be controlled for publication bias. Unlike most RCTs, naturalistic studies more frequently have non-commercial funding sources, and address correlations rather than causal relationships. Therefore less is at stake also by publishing negative results.

*2) What are the characteristics of these studies regarding location, attrition, sample size, gender, age and comorbidity?*

The majority of the controlled and extension studies were performed in United States (10/15). The RCTs had fairly large sample size at inclusion with between 200 – 500 patients enrolled. However, high attrition rates among both drug-treated and placebo-treated patients (drop-out rates from 30 to 70%), lead to some difficulty with generalizing to the entire patient population (low external validity). Both sexes were represented in the study samples, and mean age ranged between 35 and 40 years, similar to real-life clinical populations.

However, comorbid mental disorders were exclusion criteria in most of the studies with initial RCT and taking into account that in a clinical setting most patients have at least one comorbid mental disorder, this raises unresolved questions about clinical validity of the RCT efficacy findings. These characteristics of location, and restriction of comorbidities are similar to characteristics of shorter term RCT studies (Santosh et al. 2011, Torgersen et al. 2008, Faraone & Glatt 2010), as would be generally expected from studies with a RCT start. It should be relevant to perform more studies in Europe, try to limit attrition, and also include psychiatric comorbidity.

### 3) *How is effectiveness in a long-term perspective?*

All of the RCTs reported that ADHD medications were significantly more efficacious than placebo (Table 2), and in the RCTs with open label extension, the efficacy demonstrated during the placebo-controlled phase, was either maintained or further improved during the extended follow-up period (Table 3).

As indicated in the *number needed to treat* (NNT) statistics from the review (Table 2 and 3), between 4 and 6 patients need to be treated to achieve one good, medication-related, long-term treatment responder. However, the strict exclusion criteria adopted in the majority of RCTs make it difficult to generalize the results to the general clinical population, where comorbid mental disorders are the rule rather than the exception.

The naturalistic studies were found with positive correlation between treatment with central stimulants and lower frequencies of comorbid mental disorders, improved a positive educational development and employed in adulthood, and older age at treatment initiation was associated with poorer occupational outcomes, indicating benefit of early recognition and treatment. Several naturalistic studies found no link between prior pharmacotherapy for ADHD and subsequent development of substance use disorders. Findings in the open-labeled long term studies were in line with results reported in recent reviews of shorter duration studies (Torgersen et al. 2008).

Summing up the results from several studies revealed evidence for some long-term benefit of sustainment of ADHD drug treatment. High drop-out rates and low levels of comorbidity in the RCT studies limit their clinical relevance. There is also lack of head-to-head comparing trials between the drugs, so the question about their relative effectiveness is not resolved. In spite of these limitations, and with the relevant literature of long-term drug treatment primarily naturalistic, I suggest that the pharmacological treatment of ADHD

primarily leads to less ADHD symptoms, and secondly to higher educational levels and occupational status, fewer accidents, and less delinquency. This should support the recommendations of medical treatment in the guidelines concerning adult ADHD (Cornforth et al. 2010, Hazell 2004, Barkley et al. 2005, Peterson et al. 2008, Banaschewski et al. 2006, Kooij et al. 2010, Modesto-Lowe et al. 2012).

*4) How are medications tolerated, and to what degree are tolerability, adverse effects and safety reported?*

In RCTs and extension studies, the medication was well tolerated by most patients, and most adverse effects occurred during the initial titration phase. As expected adrenergic related effects such as decreased appetite, nausea, palpitations, mucosal dryness and dizziness were the adverse effects most frequent reported. There was also some risk for increases in nervousness, irritability and sleep disturbance, the most common psychological adverse effects. Most frequent short-term adverse effects are well understood due to the adrenergic effects of the stimulant compounds (Leonard et al. 2004) and atomoxetine (Arcieri et al. 2012), however, long term risk of such alterations are less studied.

It was reassuring that large epidemiologic studies of adverse effects of persons using central stimulants did not report any significant associations with increased risk for serious cardiovascular events compared to none-users (Cooper et al. 2011, Habel et al. 2011, Schelleman et al. 2012).

The RCTs and extension studies had methodological limitations. Most commonly they ran only for a short time span of 10-12 weeks in order to test efficacy, and we found only four studies lasting more than 24 weeks. Thus, the RCTs phase scarcely gives information about outcomes or safety in a long-term perspective. Although large cross-sectional epidemiological studies showed no increased risks for cardiovascular disease or death, few long term studies have examined safety, and there is need for larger scale studies over time (Murray et al. 2013).

While initiation of psychostimulants was not associated with elevated risk of serious cardiovascular events large epidemiological studies found, one recent study published after our review on amphetamines or atomoxetine could not exclude a modest elevated risks for sudden death or ventricular arrhythmia (Schelleman et al. 2013). Therefore it is still reasonable to advice that these medications should not be used with patients having pre-existing cardiac abnormalities, and cardiovascular parameters should be monitored in stimulant-treated adults with ADHD, especially those with borderline abnormal cardiovascular signs.

More recently, and after our review was submitted, some studies with retrospective design addressing issues of longer term treatment duration have been published on Norwegian samples of adult ADHD patients (Gjervan et al. 2012, Torgersen et al. 2013, Torgersen et al. 2012, Halmoy et al. 2009, Lensing et al. 2013). Torgersen et al. (2012) conducted a retrospective study of predictors for long treatment duration ( $\geq 3$  years) in a sample of adult ADHD patients utilizing data from medical records ( $n = 117$ ). The median duration of central stimulant treatment was 33 months, and use of extended-release formulations of methylphenidate predicted positively long treatment duration, whereas baseline antisocial personality disorder and comorbid substance use disorder were related to shorter duration of treatment.

In another Norwegian study performed by a retrospective questionnaire survey, Lensing et al. 2013 (Lensing et al. 2013) reported favourable outcome for 21% of the ever-treated respondents at a follow-up, with a mean observation time of 4.5 years. Those who had received treatment for more than 24 months reported larger improvements than those with shorter treatment duration. Although these studies have limitations due to their retrospective design, they add to the literature on beneficial outcome associated with continuation of ADHD medication in adult patients as well.

Despite the growing literature about the long-term effects of ADHD medications (Paper I), several issues require further study. Notably, no generally accepted definition exists for what is regarded as a long-term study, as this will obviously depend on the condition that is being treated. Previously, at the time when ADHD was considered a self-limiting developmental disorder of childhood, studies of many years duration were considered less relevant. In our review, we adopted a practical compromise, including studies down to 24 weeks of duration, as we otherwise would have been left with very little data from RCTs.

#### **4.2.2. Functional outcomes in previously untreated ADHD adults (Paper II)**

*1) Whether the number of childhood ADHD symptoms and severity of symptoms, are significantly associated with lower levels of education and long-term work disability in treatment naïve adults with ADHD?*

##### *Main findings and comparison with literature*

High levels of ADHD symptom severity in childhood measured by the WURS and higher numbers of hyperactive-impulsive symptoms in childhood measured by the DIVA were significantly related to shorter duration of basic education and dropping out of high school.

No significant sex differences were observed concerning these educational outcomes. Concerning long term work disability, neither the childhood ADHD symptom severity nor the number of ADHD symptom criteria met in childhood, showed any significant relationships to work status in adulthood.

Consistent with our findings, longitudinal studies of children with ADHD have found more severe ADHD symptoms associated with poorer educational attainment (Powers et al. 2008, Hechtman et al. 1984), and hyperactive-impulsive symptoms in particular (Barkley et al. 1990). A population-based retrospective study of ADHD compared to healthy controls, also has reported having a ADHD diagnosis in childhood was associated with poor long-term school outcomes including more drop-outs (Barbarese et al. 2007).

An explanation of this consistent finding may be that youths with high levels of hyperactive-impulsive symptoms may either be more prone to experience negative feedback in school due to their disruptive behavior, or to make impulsive decisions about discontinuation. Some studies have reported that comorbid conduct disorder was the best predictor of high school dropout (Barkley et al. 1990, Breslau et al. 2011). A longitudinal study, however, did not find such an association (Trampush et al. 2009), but differences concerning IQ level, reading ability, socioeconomic status, marijuana use, and limited parental contact significantly differentiated school-dropouts from graduates.

In our study (Paper II), when adjusted for occurrence of *antisocial-conduct behavior* (based on the MINI interview), the number of hyperactive-impulsive childhood symptoms remained a statistically significant predictor of high school drop-out, and this may indicate that school interruption is to some degree related to hyperactive-impulsive symptoms.

Almost twice as many patients in our total sample (56%) as in the general Norwegian population (33%) had not completed high school. Compared with two other Norwegian studies, patients in our sample was lower educated than the 48% reported by Gjervan et al. (2012) and 29% observed by Halmøy et. al (2009). Longitudinal studies of children with follow-up into early youth and young adulthood have found similar adverse educational outcomes associated with the severity of childhood ADHD symptoms (Barbarese et al. 2007, Barkley et al. 1990).

Numbers of childhood inattention and hyperactivity-impulsivity symptoms were examined separately. When statistically significant associations by univariate analyses were found, these factors were included in an adjusted analysis, and hence the described findings (Paper II). Prior to our study, reports of adult outcomes have examined associations to adult



subtype categories and scores of ADHD rating scales in adulthood, but not to childhood.

Our study was able to correlate the severity of childhood ADHD symptoms and a high number of childhood hyperactive-impulsive symptoms with school dropout and interrupted education. We also noted that adult inattentive symptoms were associated with occupational impairment and that adult comorbidity 'predicted' work disability. In contrast to prior literature with similar findings, our analyses were dimensional as per current DSM trends. A dimensional approach to symptoms and behaviors rather than categorical, was useful to elucidate aspects of ADHD such more like a spectrum disorder.

Although, we found that childhood symptoms and characteristics were related to less favorable educational outcomes, these factors seemed weekly to influence on the other outcome of *being out of work last year*. The lack of significant correlations between level of childhood symptoms and being one-year out of work, suggests that differences in employment and long term work disability among ADHD adults are not directly related to differences in childhood ADHD or educational deficits.

Weak significant correlations between specific ADHD symptoms and impairment have been reported previously. In a study based on two longitudinal case-control study samples (Gordon et al. 2006), measures based on symptoms accounted for less than 10% of the variance in measures of impairment. Another more recent study based on a follow-up of ADHD children sample has reported statistically significant relationships between childhood ADHD symptoms and impairment in adulthood, when impairment in ADHD tied functional domains was evaluated (Mannuzza et al. 2011). In this study the measure of impairment was not limited to behavior in any particular area as education or work; instead a clinical evaluation of impairment was rated according to answers to the interview questions: "Have [SYMPTOMS OF ADHD] led to any difficulties at home, at work, or with other people? ...For example, have these behaviors diminished your performance at work, or interfered with doing things at home, or affected your relationships with friends?" These impairments were assumed to be more closely tied to the ADHD than a global index of functioning, but may be influenced by the patient attribution.

In our Study II, we applied defined impairment measures of educational and vocational outcomes not supposed to be directly influenced by patient attribution. Requirements of impairment are integrated in the DSM-IV-TR ADHD syndrome (by criterion C and D) (Table 1), but regardless of these, we did not simply ask the question are these two domains of education or work impaired in adult ADHD? Rather, we assessed whether this

level of disability in adulthood was related to number of childhood criteria met, and that is, to our knowledge, a novel contribution to literature.

### *Implications*

Our findings of educational and vocational impairments in adult patients diagnosed with ADHD correspond with previously results from follow-ups of children with ADHD into youth and young adulthood. Less was known about childhood factors in previous non-medicated adult patients diagnosed in adulthood, and our examination of dimensional relationship between childhood ADHD symptoms and adult functional outcomes adds to the literature on ADHD adults. Our findings indicate persistence of particularly impairing inattentive symptoms of the ADHD syndrome in adulthood

It was surprising that low degree of education did not correlate significantly with long-term work disability in our study, since education can be a prerequisite for obtaining employment. In the Paper II, education is discussed being of less importance in our sample; both patients with low and high educational achievements may become work disabled for other reasons, as well. Also, some factors that could have compensated for lack of education are suggested (workplace facilitations and open labor), and these hypotheses could be further studied.

### *Limitations*

Limitations by use of retrospective determination of childhood symptoms, and the relatively crude categorical outcome measures should be considered. Problems with retrospective diagnostics and recall bias are discussed above (Section 4.1.2).

The defined categorical functional outcomes of *dropping-out of high-school* and *being out of work last year*, may be influenced by various conditions, not only ADHD behaviours. These outcomes also lack information about the mode of impairment of each patient; data that could be essential to understand impact of ADHD and other conditions on these outcomes. Furthermore, those patients with most hyperactivity-impulsivity in childhood related to interrupted schooling, were also most severe affected (had more symptoms and higher score on the WURS), and had accompanying high levels of inattentive symptoms as well. Intercorrelations between number of childhood inattention and hyperactivity-impulsivity symptoms made some difficulties to separation between these dimensional symptoms in the analyses.

*2) Whether the observed associations are moderated by persisting ADHD symptoms in adulthood, gender and comorbidity?*

*Main findings and comparison with literature*

A large percentage (56%) of our sample had not completed secondary school equivalent to high school, and no significant difference between the sexes was observed for this finding. Moreover, statistically significant more males than females were in paid work, and more females than males had disability or rehabilitation pension. Work status was not significantly related to differences in ADHD characteristics in childhood. However, adult number of inattentive symptoms (the DIVA), adult high levels of ADHD inattention-symptoms (the ASRS inattention subscale), and number of comorbid disorders (the MINI), were related to likelihood of being work disabled last year by logistic regression modeling.

It has previously been reported that hyperactive-impulsive symptoms decrease by age, while inattentive symptoms tend to persist into adulthood (Faraone et al. 2006a). In a cross-sectional and retrospective study Kessler et al. (Kessler et al. 2010) reported that inattentive symptoms were more persistent into adulthood than hyperactive-impulsive symptoms, and the strongest predictor of ADHD persistence into adulthood was childhood ADHD symptom severity. This could lead to more severely childhood affected individuals with inattentive impairments among the ADHD persistent adults, and do in fact correspond with our findings of more inattentive symptoms among the patients long-term out of work.

Logistic regression modeling, after adjusting for age and gender, showed an association between number of persistent inattentive symptoms (the DIVA) and corresponding adult high levels of ADHD inattention-symptoms (the ASRS), and the likelihood of being long term work disabled. The modeling also revealed a relationship between number of comorbid disorders and this likelihood of being work disabled last year. This could be interpreted as both adult ADHD inattentive symptoms and comorbidity contributed significantly to the functional impairment.

Our findings were consistent with report from another Norwegian study published after our study was started; Halmøy et al. (2009) which reported that comorbid substance abuse, depressive, or anxiety disorders in adulthood were significantly associated with being out of work. However, they found no statistically significant relationship with high frequencies of self-rated inattentive symptoms (ASRS), but reported increased risk for unemployment by belonging to the ADHD-combined subtype, though levels of inattentive

scores (ASRS) for the sub-type categories were not available from the paper. Gjervan et al (2012) in another study from Norway, found that higher current inattentiveness (ASRS) was significantly related to fewer days at work in adults with ADHD. In our Study II persistent inattentive symptoms both by self-rating (the ASRS) and investigator assessed behaviors (the DIVA) were related to long term work disability. This was in line with other reports stating that the inattentive and not the hyperactive-impulsive symptom cluster, is the most disabling aspect of adult ADHD (Sobanski et al. 2008, Stavro et al. 2007).

We found a weak but non-significant trend for possible association between educational failure and long term work disability. Halmøy et al. (2009) however, reported that lower level of education significantly predicted unemployment. These different findings may be explained partially by the fact that in our region at the time of the study, the level of unemployment was low implying a need for unskilled workers.

Other studies have reported higher as well as lower non-working rates (Able et al. 2007, Sobanski et al. 2008). In our sample almost twice as many women as men were fully out of work last year due to disability, and this difference remained statistically significant when adjusted for age and comorbidity. The same tendency, though not statistically significant, was found in two other Norwegian samples (Halmoy et al. 2009, Gjervan et al. 2012). This significant gender difference could indicate that females are more vulnerable than males to the disabling consequences of ADHD in a vocational context, or more prone to get work environments particularly less compatible with ADHD. This raises unresolved questions about unfavorable environmental work place factors, and indicates needs for counselling or facilitation, as well as it challenges for further research.

A large proportion of our sample also had other mental disorders (75%), and this is consistent with prevalences reported in other studies on adult ADHD (Torgersen et al. 2006). The total number of comorbid disorders did not differ significantly between the sexes, or between those who did and did not complete high-school. Adult comorbidity of mental disorders was significantly related to long-term work disability in our sample, independent of sex.

Several studies have shown more impaired functional outcomes in adolescents and young adults for patients with childhood ADHD with co-occurring conduct or substance use disorders in childhood compared to peer ADHD patients without such comorbidity (Hinshaw 1992, Hurtig et al. 2007, Mannuzza et al. 1993). Similar findings of greater adult impairment related to a broader spectrum of comorbidity in adulthood including anxiety and depression

have previously been found for adults with ADHD (McGough et al. 2005, Mick et al. 2008, Weiss et al. 2010). Our results correspond with a significant literature showing that psychiatric morbidity in general is associated with work disability in adults (Lorant et al. 2003, Virtanen et al. 2011, Sareen et al. 2006). A significant proportion of the patients (71%) in our sample used or had used last year, a medication for anxiety or depression at admission, mostly antidepressants (> 90% of the drugs). The use of these medications was associated with long-term work disability. The most obvious explanation to this is that the patients using these medications have comorbid mental disorders that contribute to their work disability.

#### *Contribution to literature and implications*

Our findings emphasize the serious consequences of ADHD in childhood and adulthood in terms of functional outcomes such as school drop-out and long-term work disability. These findings may suggest that earlier recognition and intervention for ADHD and adequate treatment of comorbid mental disorders are of importance to improve the long-term outcomes for ADHD patients. Our dimensional approach revealed the importance of addressing inattentive symptoms in the treatment of adult ADHD, and calls for further research on work rehabilitation and adequate workplace measures to prevent long-term work disability.

#### *Strength and limitations*

The strengths and limitations of the prospectively included patient sample of treatment naïve, adult ADHD patients, representing a wide age-span, both sexes and comorbid mental disorders are discussed in the above section of general methodological issues (Section 4.1.2). Our findings should be considered within the limitations of the design and methods applied; it is primarily a combined cross-sectional and retrospectively designed study based on data from a clinical sample. Furthermore, investigators were not blind to the participants' diagnostic status, which could have influenced their assessments.

Our findings of statistically significant associations do not imply causal relationships. Interpretations of relationships in the regression analyzes, imply reasonably theoretically overview of possible confounding factors. Adjusting for age and gender was a reasonable choice, but also problems with intercorrelation should be mentioned, due to limitations of implementation several inter-related factors in the model simultaneously.

We did not perform the analyses of the conventional DSM-IV ADHD subtype categories because the current DSM-IV methods for defining subtypes have been heavily

criticized for lack of stability over time (Lahey & Willcutt 2010)(see Section 1.3.). For this reason, we examined ADHD behavior symptoms using dimensional symptom scores (by the DIVA).

#### **4.2.3. Outcomes following one year of drug treatment (Paper III)**

*1) How is the effectiveness including tolerability after one year of drug treatment of previously drug-naïve adult ADHD patients, with methylphenidate being the first-line medication?*

##### *Main findings and comparison with other studies*

Above ninety percent of the patients completed examination at the 12- month follow-up, and many of these (70%) continued being medicated, mostly on methylphenidate (80%). Those patients who remained on any ADHD drug had a significant improvement of primary (the ASRS and the GAF) and secondary outcome measures (the CGI-I and the SCL-90) at one year follow-up compared to their not medicated baseline, and with significant greater improvement compared to those who discontinued medication (Figure 1). Furthermore, frequencies of adverse effects were generally low. Of the patients (28%) who had discontinued medical treatment before 12- month follow-up, just under half terminated due to side-effects (n = 31), and no serious adverse events were recorded.

The significant reduction of ADHD symptoms is consistent with published RCTs and extension studies on the long-term effectiveness of single ADHD drugs in more selected patient samples ( Adler et al. 2009a, Adler et al. 2008, Biederman et al. 2010a, Rösler et al. 2009, Young et al. 2011). The improvements of global severity and function and the reduction of mental distress (GSI) also correspond well with broader outcomes found in studies exploring such characteristics (Wender et al. 2011, Weiss et al. 2010, Ginsberg & Lindefors 2012, Adler et al. 2009b).

Sustained and increasing improvement during the first year has also been reported previously for dexamethylphenidate and atomoxetine (Adler et al. 2009b, Marchant et al. 2011), and in that case our findings replicated this interesting course for a broader patient population and on a current drug regime. Notably, partly non-adherent patients in our study (Paper III) had effectiveness outcomes that were intermediate between the fully compliant and non-medicated groups. This may be explained by partial responses related to lower degree of

adherence, and indirectly support assumptions of long term effectiveness of current ADHD medication. Our results of 70% one-year completion on-medication are in line with the findings in another Nordic prospective observational study (Bejerot et al. 2010), and should support the assumption that many patients benefit from the ADHD drug treatment.

We observed no serious adverse effects corresponding to reports from studies cited in the review. Noteworthy, measures of cumulated adverse effects over time (the CADDRA) (Canadian ADHD Resource Alliance 2011) showed an inverse relationship with the effectiveness outcomes. Reasons for termination of medication included adverse effects, such as palpitations, mood instability, nausea, agitation, and anxiety. This fits well with other studies on safety and tolerability (Adler et al. 2011, Bejerot et al. 2010, Buitelaar et al. 2011), and may be expected from knowledge of the adrenergic effects of the pharmacological compounds used. Most patients experienced mild adverse effects, and less than half of those who discontinued medication did so due to adverse effects, and mostly terminating early. Still, the finding of nine patients with increase in blood pressure exceeding the safety limits, all of them with borderline elevated blood pressure at baseline, should be taken into account in clinical practice. Also several patients who continued on medication had slightly increased heart rate, and the long-term consequences of such persistent adrenergic effects are not known (Vitiello et al. 2012). We found no significant change in the ECGs, including QTc, following treatment, in line with another study on methylphenidate (Marchant et al. 2010). Though, we may expect such changes to be of low prevalence affecting particularly vulnerable patients. For this reason studies of larger samples should be conducted.

### *Implications*

Though, our findings may be seen as replications of results from the previous small number of intermediate and one-year RCT-extension studies, our study complement such findings on a broader clinical sample, including comorbid patients and patients with various medication dosages and adherence, and to some extent our model adjusted for such confounding factors in treatment. In a specialized outpatient setting application of a current medication regime for ADHD adults was associated with long-term reduction of ADHD symptoms and improvement of function and mental distress among those who used the medication, and adverse effects were within expected incidences. These results may provide realistic guidance for clinicians with regard to medical treatment in everyday practice, and should supplement previous knowledge regarding the effectiveness of ADHD medication regimes.

### *Strength and limitations*

This is a large single-site clinical cohort prospective study on medication-naïve adults, and the study was implemented in a specialized outpatient setting. Over ninety percent of the patients completed evaluation at one year follow-up, and about seventy percent out of these remained on medication. We were able to follow prospectively a large clinical cohort with ADHD adults, and with a low proportion of drop-outs, we achieved a clinical relevant basis for longitudinal analyzes.

Given the nature of open-label uncontrolled design, causal relationships between medication and outcome measures cannot be drawn. In the prospective observational study (Paper III) we have discussed the inherent limitations of using an open-label design. It is thereby possible that patients were inclined to overestimate treatment effectiveness. The blinding of previous assessments and responses to questionnaires are not considered to compensate fully for this bias. The applied medication regime, with a low proportion of patients using atomoxetine, also precluded comparisons of effectiveness between different drugs. However, we found that patients using atomoxetine as a second-line medication, if stimulants were not effective or tolerated, had a significantly higher responder-rate than those who discontinued drug treatment.

### *2) Are outcomes moderated by age, gender, dosage, side-effects, or comorbidity?*

#### *Main findings and comparison with other studies*

The differences in effectiveness between being on and off medication appeared early on in treatment, with an overall increase during the follow-up visits, and higher dose of medication was associated with greater improvement, while adverse effects and comorbidities were related to less effectiveness (Paper III).

We found a greater improvement in ADHD symptoms for males than for females, in contrast to some other studies reporting no sex differences (Rosler et al. 2010, Wender et al. 2011), or even greater improvement for females on measures of emotional dysregulation (Marchant et al. 2010). However, we found no sex differences on the global GAF-measures or for mental distress, and adherence at endpoint did not differ between the sexes, similar to reports by a three- year retrospective study (Torgersen et al. 2012).

Comorbid anxiety and bipolar disorders were associated with less effectiveness adjusted for age, gender and dosage. Retrospective studies have found comorbidity related to



less adherence to medication (Lensing et al. 2013, Torgersen et al. 2012), and this corresponds with our findings with less comorbidity among those adherent to treatment.

Medication dosages were in line with other medication studies in adults with ADHD (Wender et al. 2011, Adler et al. 2011, Marchant et al. 2010). Similar to what was reported in a study from a younger patient population (aged 9 - 21 years) (Powell et al. 2011), we found variations in dosages across time and individuals, although patients with highest dosages tended to have the best responses. The flexible dose regime allowed for individualized dosing, thus taking into account both tolerability and optimizing efficacy.

### *Implications*

To our knowledge, this is the largest single site prospective study of adult ADHD patients. In a general clinical setting we found sustained and increasing improvements of patients correlated with time on ADHD drug treatment. Higher dosage of medication over time was associated with greater improvement. Though, adverse effects and comorbidities were related to less effectiveness of treatment, the benefit of treatment was not essentially weakened for most of the patients during one-year treatment. These findings supplement previous knowledge regarding the effectiveness of ADHD medication regimes. Although most patients reported improvement on medication, a significant proportion did not respond properly or did not tolerate any of the current drugs. Further research is warranted on these subgroups of patients. There is also a need for developing more specific treatment programs for patients with comorbid mental disorders. Psychosocial treatments are also available, and the combination of pharmacological treatment and psychotherapy is another important theme for future studies.

### *Strength and limitations*

In the longitudinal analyses, time variation confounding is a source of bias not fully accounted for in our linear mixed model (LMM). Also, “the missing values at random” assumption in the LMM is questionable, even though loss to follow-up was small and partly adjusted for by cumulative amount of adverse effects. In spite of the estimated treatment effect falling short of a “true” causal effect, the LMM was considered to be a reasonable choice, with its widespread recognition and ability to address, at least partly, the problems of confounding and loss of patients to follow-up. A dose-response effect of treatment was found

to be strong, even in the presence of the additional time covariates, which should yield a conservative estimate.

## 5. Conclusions

At the time of our review (Paper I), treatment of adult ADHD with stimulants and atomoxetine had shown beneficial effects in a few RCTs up to six months follow-up, and was well tolerated among most of the patients. However, more systematic studies with longer observation time are needed to indicate whether these findings are clinically relevant in longer time perspectives.

Childhood hyperactive-impulsive symptoms and overall severity of childhood ADHD-symptoms are associated with high school drop-out rates, while persisting inattentive symptoms and comorbid mental disorders in adulthood are more related to occupational impairment (Paper II).

One year treatment of adult-ADHD with stimulants or atomoxetine was associated with clinically significant reduction of ADHD-symptoms, improvement of function and reduction in mental distress. No serious adverse events were observed, and side-effects in general were acceptable (Paper III). Recognition and pharmacological treatment of adult ADHD seem beneficial for the most patients.

## 6. Future perspectives

### *6.1. Implications for clinical practice*

Although the relevant literature identified in the review was scarce and primarily naturalistic, it suggests definitively that the pharmacological treatment of ADHD leads to symptom reduction, better self-esteem, higher educational levels and occupational status, fewer accidents, and less delinquency. This should support the recommendations of medical treatment in the current guidelines. Though we found no association between stimulant treatment and sudden cardiac death (Paper I), these drugs should be used with caution, and cardiovascular parameters should be monitored in stimulant treated adults with ADHD,

especially those with borderline abnormal cardiovascular signs. Furthermore, because stimulants may be abused, their potential for causing substance abuse has been a concern. Although meta-analyses, mainly in younger populations, have shown that stimulants do not increase the risk for substance use disorders, clinicians should be alert to the risk for misuse and diversion among ADHD adults.

The close relationship between severity of child ADHD symptoms and a high load of hyperactive-impulsive symptoms in childhood ADHD, and drop-out from school and fewer years of attained education (Paper II), suggest that early recognition and intervention for ADHD may be essential for improving the long-term educational outcomes of ADHD patients. Findings of persistent inattentive symptoms in adulthood and additional adult comorbidity, associated with greater occupational impairment, which were major predictors of long term work disability, should be emphasized in the treatment measures of adult ADHD. Measures and counseling towards workplace adaptations to prevent long-term work disability are warranted. A dimensional approach (Paper II) actualized a perspective on ADHD as a spectrum disorder, and challenged “well-defined” diagnostic categories in the understanding of this psychiatric disorder and its relation to impairments. Patients with a categorically “sub-threshold” ADHD diagnosis may benefit from treatment interventions as well, and symptom overlapping comorbid diagnoses may not be seen as a hinder for ADHD diagnosis or treatment.

In our study on medical treatment (Paper III), medication for adult ADHD was associated with long-term reduction of ADHD symptoms and improvement of function and mental distress among those who used the medication, and side-effects were within expected incidences. These results should provide realistic guidance for clinicians with regard to medical treatment in everyday practice, and should supplement previous knowledge regarding the effectiveness of ADHD medication regimes.

## ***6.2. Implications for future research***

There is still a shortage of long term studies, and treatment effects should be studied for years rather than months (Paper I). For inferences of causal associations between treatment and outcomes, the RCT design is the preferred methodology. However, at the current state, this appears not to be feasible. Concrete and simple outcome variables, on large samples with less exclusion criteria, may be preferable to sophisticated psychological measures with unclear

ecological validity. Thus, information from prescription databases, linked to health registers could give information on a sample size and time scale not available for conventional RCTs.

In many areas of medicine, the ethical issues involved in performing long term RCTs are currently being discussed. That leaves us with open-label extensions and naturalistic studies along with their concomitant biases and confounds similar to what is discussed in relation to our Paper III. In ADHD treatment, as well as in many other therapeutic areas, health economic perspectives of the interventions are increasingly being requested and discussed. It is expected that a treatment method should contribute to a measurable increase in quality adjusted life years or other measures of long-term benefit. Few of the studies cited in our review contain such data.

Another limitation of current long-term studies has been the focus on ADHD symptoms as a measure of efficacy. Although such data are essential, clinicians and patients ultimately are more concerned about the functional implications of treatment. For this reason, future research should incorporate measures of functional outcomes. It should also evaluate the degree to which the patient's symptoms and behaviors have been optimized, rather than simply evaluating a fixed response criterion. More suitably, the goal of ADHD treatment should be clinically relevant remission of symptoms and impairments and this should be implemented in the research protocols to address these goals (Ramos-Quiroga & Casas 2011).

Our dimensional approach (Paper II) revealed the importance of addressing inattentive symptoms dimensionally in the understanding of adult ADHD, and calls for further research on relationships with functional outcomes, prevention of work disability and rehabilitation.

Although most patients reported improvement on medication (Paper III), a significant proportion did not respond properly or did not tolerate any of the current drugs. These subgroups of patients are suggested to be subject of further studies. There is also a need for developing more specific treatment programs for patients with comorbid mental disorders. Psychosocial treatments are also available, and the combination of pharmacological treatment and psychotherapy is another important theme for future studies.

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## **Original paper I - III**













# ADHD Attention Deficit and Hyperactivity Disorders

## Childhood and persistent ADHD symptoms associated with educational failure and long-term occupational disability in adult ADHD

--Manuscript Draft--

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<b>Abstract:</b>	<p><b>Abstract</b></p> <p>Few studies have examined the impact of childhood ADHD symptoms on adult ADHD functional outcomes. To address this issue dimensionally, ADHD symptoms in childhood and adulthood and their relation to educational deficits and work disability are studied in a clinical sample of adult patients with previously untreated ADHD.</p> <p>Method: 250 adults diagnosed systematically with ADHD according to DSM-IV were prospectively recruited. Primary outcomes were high school dropout and being out-of-work-last-year. Childhood ADHD-symptoms, sex-differences, comorbidities of other mental disorders and adult ADHD symptoms were examined by historical data, clinician interviews and questionnaires.</p> <p>Results: High levels of ADHD symptom severity in childhood were related to dropping out of high school (odds ratio = 3.0), as were higher numbers of hyperactive-impulsive symptoms in childhood. Significantly more women than men were long-term work-disabled (odds ratio = 2.0). After adjusting for age and gender, persisting high levels of ADHD inattention-symptoms in adulthood (odds ratio = 2.5), number of comorbid disorders, and particularly anxiety-disorders, were significantly related to long-term work disability.</p> <p>Conclusion: Childhood hyperactive-impulsive symptoms and overall severity of childhood ADHD-symptoms were associated with high school drop-out rates, however persisting ADHD inattention symptoms and comorbid mental disorders in adulthood were more correlated to occupational impairment. These findings underline proposals for studies on early recognition and interventions for ADHD and psychiatric comorbidity. They further suggest that inattentive symptoms be a focus of adult ADHD treatment and that workplace interventions be considered to prevent long-term work disability.</p>

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## Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a childhood-onset neurodevelopmental condition characterized by age-inappropriate levels of inattention, hyperactivity and impulsivity (Kooij et al. 2010). Numerous follow-up studies have confirmed the persistence of ADHD symptoms into adulthood (Barkley et al. 2002; Biederman et al. 2012; Biederman et al. 2011; Fayyad et al. 2007; Kessler et al. 2005a; Kessler et al. 2006; Lara et al. 2009; Mannuzza et al. 2003; Kooij et al. 2005). Adolescents and young adults with childhood ADHD have significantly poorer academic achievement and work performance compared with those who did not have ADHD as children (Barkley et al. 2006; Mannuzza et al. 1993; Hechtman et al. 1984). As adults they also have more comorbid mental disorders including drug and alcohol abuse (Hechtman and Weiss 1986; Biederman et al. 2006). Childhood onset, persistent adult ADHD thus seems to have serious long-term consequences (Able et al. 2007; Adler 2007; De Graaf et al. 2008; Kessler et al. 2005b). Poor academic achievement and long-term work disability may be considered particularly relevant for adult functioning due to their widespread social, financial and personal consequences (Biederman et al. 2008).

To date several studies of adult ADHD outcomes have reported on categorical ADHD subtype differences (McGough et al. 2005; Millstein et al. 1997; Murphy et al. 2002; Sprafkin et al. 2007). Sobanski et al. (2008) reported no significant differences between the subtypes concerning functional outcomes; all ADHD subgroups had significantly less education, were more frequently unemployed and had more lifetime psychiatric comorbidity compared with non-ADHD controls. Accordingly, Murphy et al. (2002) reported that compared with community controls without ADHD, both the combined ADHD subtype and the inattentive subtype had significantly less education, lower proportion of graduation from college, and they were more likely to have received special education in school. On the other hand, Halmøy et al. (2009) found some differences between the subgroup categories. In their sample only 24% of adults with ADHD were gainfully employed, compared with 79% of population-based controls, and they reported comorbid substance abuse, depression, or anxiety disorders and belonging to the ADHD-combined subtype, were significantly associated with being out of work. In contrast, Gjervan et al (2011) found that higher current inattentiveness in adulthood was significantly related to fewer days at work in adults with ADHD.

However, categorical approaches to study subtype have been questioned. A considerable literature shows that DSM-IV childhood ADHD subtypes lack stability over time (Lahey et al. 2005; Nigg et al. 2010). Also, there is an age-dependent tendency for hyperactivity and impulsivity (H/I) symptoms to decline at a higher rate

than inattention (In) symptoms during childhood (Faraone et al. 2006a). Therefore, in the context of predicting adult outcomes, examining the number or accumulated load of In- and H/I- symptoms along with total symptom-severity in childhood may be more appropriate than subtype-categories (Lahey and Willcutt 2010).

Few studies of patients diagnosed with ADHD in adulthood also assessed ADHD symptoms in childhood. In a prospective, follow-up study of males diagnosed with ADHD in childhood, Mannuzza et al. (2011) reported that a high number of ADHD symptoms in adulthood were associated with increased impairment in adulthood. In a retrospective study, Kessler et al. (2010) found that In-symptoms were more frequently persistent into adulthood than H/I-symptoms; the strongest predictor of ADHD persistence into adulthood was childhood ADHD symptom severity.

Differences between the sexes regarding adult outcomes are of particular interest. Unlike studies of childhood ADHD, which report a greater preponderance of males, gender ratios tend to be equal in studies of adult ADHD (Barkley et al. 2010; Faraone et al. 2006b). Some studies find that more women than men are diagnosed with ADHD in adulthood (Groenewald et al. 2009), and that women are less frequently diagnosed with H/I-symptoms in childhood than males (Rucklidge 2010). Girls with ADHD are also reported to suffer from internalizing symptoms of anxiety and depression and comorbid mental disorders more frequently than boys (Staller and Faraone 2006), although it is questionable whether these differences are maintained in adulthood (Quinn 2008). In a study of adult ADHD, Grevet et al. (2006) found no significant sex differences as regards ADHD subtypes or psychiatric comorbidity. Another study of adult ADHD (Rasmussen and Levander 2009) reported that substance abuse and criminality were more prevalent among men, and affective, eating, and somatization disorders more common among women. However, ADHD symptom severity and subtype did not differ between the sexes. Unlike these results, women were more affected than men on different ADHD-scales in another retrospective study (Robison et al. 2008).

In summary, most studies of adult ADHD have studied ADHD symptoms in adulthood, and the reported relations between ADHD symptoms and functional outcomes such as education and work status have not been consistent. Few studies of adult ADHD have specifically examined childhood ADHD symptoms dimensionally, and their ability to predict educational attainment in adults with ADHD (Gau 2011), and there is a sparse and ambiguous literature about predictors of long term work disability. More research in the area could suggest how to prevent educational failure and occupational impairments and provide directions for further research. Therefore, the aims of our study were to examine whether the number of assessed childhood ADHD symptoms and ADHD symptom severity were associated with lower levels of education and long-term work disability in

clinically referred treatment naïve adults with ADHD. Further we sought to examine whether these associations were moderated by persisting ADHD symptoms in adulthood, gender and comorbidity.

## **Methods**

### Site and sampling

The present study is part of an ongoing prospective observational study of the medical treatment of adults with ADHD at the Outpatient Clinic at the Division of Mental Health and Addiction, Vestfold Hospital Trust, Norway, which is located in the South-Eastern part of Norway, and covers a region of about 250,000 adult inhabitants. Most individuals suspected of adult ADHD within that region are referred to the clinic. Referred patients aged 18 to 60 years were recruited consecutively. For inclusion, the subjects had to fulfill DSM-IV criteria for ADHD which involve determining the presence of ADHD symptoms during both childhood and adulthood.

The exclusion criteria were any clinically unstable mental disorder that needed immediate treatment, any medical contraindications for stimulant treatment such as hyperthyroidism, cardiovascular diseases or cardiac arrhythmias, patients having previously tried stimulant medication in adulthood or during the prior five years for patients 18 years of age. We also excluded patients with an Intelligence Quotient (IQ) under 70 based on the Wechsler Adult Intelligence Scale IV (Wechsler 2008).

During the ascertainment of participants 620 referred patients were assessed for eligibility (May 2009 to December 2010). The mean age of the females ( $n = 283$ ) was 32.4 ( $SD = 10.9$ ) years, and for males 31.5 ( $SD = 10.7$ ) years. By evaluation for inclusion 262 patients (42%) were eligible. Twelve did not consent to take part, leaving a total of 250 stimulant naïve adult patients for the study.

### Procedures

To obtain diagnoses, two board-certified psychiatrists examined each patient for inclusion criteria. The ADHD diagnosis was ascertained by a multistage and multisource procedure according to DSM-IV-TR criteria (American Psychiatric Association 2000; Barkley 2008; Faraone et al. 2006b; Haavik et al. 2010) with:

1) *The structured Diagnostic Interview for ADHD in adults, second edition (DIVA 2.0)* (Kooij and Francken 2010). To be diagnosed with ADHD, patients must have endorsed at least 6 out of 9 DSM-IV symptoms of inattention and/or hyperactivity/impulsivity in childhood, and currently have at least 6 out of 9 DSM-IV symptoms of inattention and/or hyperactivity/impulsivity for the last 6 months, and describe a chronic course from childhood to adulthood. We also included patients with 5 out of 9 symptom criteria for each symptom domain in adulthood if they had met full symptom criteria in childhood. Patients meeting the lower diagnostic threshold would be diagnosed as ADHD NOS in DSM-IV, but would be diagnosed with full threshold ADHD in DSM-5 according to the revised requirements for adult diagnosis (American Psychiatric Association 2013). We required that symptoms currently caused clinically significant impairment in social, academic, or occupational functioning.

2) To examine comorbid mental disorders and whether the ADHD symptoms might be better explained by another psychiatric disorder, *the MINI International Neuropsychiatric Interview Plus (M.I.N.I.-Plus)* was conducted by the clinicians. It is a structured diagnostic interview for DSM-IV Axis I disorders (Sheehan et al. 2002; Sheehan et al. 1998) for assessing comorbidity. 3) *Supplementary data* to support evidence of childhood symptoms were collected where available from *other informant sources* such as school records, educational psychology services in school and questionnaires rated by the parents (83% of the patients), blinded for other informants' ratings. Collateral information about current symptoms and impairment were also obtained in the majority of cases from a close relative invited to participate during the DIVA interview with the patient.

During a pilot period 21 adult patients were independently examined by two psychiatrists. For the ADHD DSM-IV diagnosis, *Cohen's kappa coefficient* was 0.77; *kappa* was 0.88 for ADHD hyperactive-impulsive criteria and 0.70 for inattention criteria. For the clinicians' assessments of comorbid mental disorders into the applied diagnostic categories of the M.I.N.I.-Plus, measure of agreement showed a *kappa coefficient* of 0.79.

### *Definition and measures of outcome*

Our two primary outcome measures were: 1) *Low level of education* defined as *not completed high school* by drop out from or interruption of the expected course of education before ending a secondary school program equivalent to high school including vocational school programs, and 2) *Long term work disability* defined as being out of work in the past year, by being fully out of paid work, ordinary school or studies due to disability for the last 12 months before enrollment in the study. Data on education were supplemented with historical data collected from school grades, and these measures were ascertained by face-to-face interview with the patients.

Because DSM-IV ‘subtypes’ of ADHD have been criticized (Nigg et al. 2010; Willcutt et al. 2012), and the DSM-5 renames ‘subtypes’ as ‘presentations’, we decided to investigate the predictive ability of ADHD symptom dimensions rather than subtypes. Assessments by the DIVA 2.0 allowed for clinician evaluation of symptom criteria of childhood and adulthood separately. Other factors studied in relation to the two main outcome variables were risk to get into fights, antisocial traits, learning difficulties, ratings of child and adult ADHD symptoms, and clinicians’ investigation of current comorbidity.

### *The Wender Utah Rating Scale (WURS)*

To identify the severity of retrospective childhood ADHD symptoms, patients rated the Norwegian short version of the WURS-25 (Ward et al. 1993; Wierzbicki 2005), a retrospective dimensional measure of ADHD symptoms which has good psychometric properties (Caci et al. 2010; Fossati et al. 2001; McCann et al. 2000; Retz-Junginger et al. 2003). The WURS-25 items are rated on a 5-point severity scale (score range from 0-100). We categorized the scaled ‘WURS-25’ (median = 56, mean = 56,  $SD = 16.9$ ) into the ‘WURS-25 category’ by quartiles (score < 40 or ‘low’, score 40 – 70 as ‘moderate’ and score  $\geq 70$  as ‘high’). The WURS subscales for *medical problems* and *school problems* were also examined.

### *Adult ADHD Self-Report Scale version 1.1 (ASRSv.1.1)*

Current adult ADHD symptoms present for last six months were dimensionally rated by the Norwegian version of the 18 item ASRSv.1.1 (Kessler et al. 2005c) The ASRS covers the nine inattentive criteria and nine hyperactive-impulsive criteria according to DSM-IV (Adler et al. 2006; Kessler et al. 2007; Murphy and Adler

2004). We used the continuous scoring method (Kessler et al. 2005c). Symptoms are self-rated on a 5-point scale of frequency with a score range of 0-72 points for total symptom load. The inattentive and hyperactive-impulsive subscales each have a range of 0-36 points. The 18 item ASRS in our sample showed a *Cronbach's alpha coefficient* of 0.86; the inattention and hyperactivity-impulsivity subscales had *alpha* values of 0.73 and 0.80, respectively.

#### *Additional information*

Historical data about pedagogical assistance in primary school, reading or arithmetic problems, grades from school reports, relevant information from other sources on childhood symptoms such as school records and psychological-pedagogic services records, were also collected systematically. Physical examination was performed by the patients' regular physician within the past three months to exclude somatic diseases and data from medical records of previous medication were collected

To evaluate intellectual ability all patients with school grades below average were screened by the Hayes Ability Screening Index (HASI) (Hayes 2000; Sondenaa et al. 2011). Exclusions of those with an Intelligence Quotient (IQ) under 70 were based on the Wechsler Adult Intelligence Scale IV (Wechsler 2008), which was performed when for HASI score less than or equal to 85.

#### Ethics

The study was approved by The National Committee for Research Ethics of the Health Region South-East and The Norwegian Social Science Data Services and have therefore been performed in accordance with the ethical standards in the 1964 Declaration of Helsinki and later amendments. After a complete description of the study was provided to the subjects, all participants gave written informed consent prior to their inclusion in the study.

#### Statistical methods

All statistical analyses were carried out by The PASW statistics (version 17) for Windows package. Data from the clinician administered MINI on comorbid mental disorders are aggregated within each diagnostic category



presented such as any panic disorder or obsessive compulsive disorder are represented as any anxiety disorder. The data were initially analyzed by descriptive methods. On the group level, categorical variables were analyzed using the chi-square test, and stratified in order to explore sex effects (Grevet et al. 2006). Testing differences in the continuous outcomes was done with t-tests when the assumption of normal distribution was met, and otherwise with non-parametric tests. The level of significance in the univariate analyses was a priori set at  $p < 0.01$  due to numbers of tests planned. All tests were two sided. The continuous scores of the WURS-25 and ASRS inattention subscale were categorized into *low*, *moderate* and *high* level by the quartiles to get a more clinically relevant representation.

Analyses of the dependent categorical factor ‘not completed high school’ were adjusted for gender, but not the ‘age’-factor because predictors should antecede the predicted factor. The work status category analyses was conducted adjusted for both age and gender. The specified independent variables found to have significant associations to the dependent variable were entered into in logistic regression models initially unadjusted one at a time, and were finally adjusted by entering age and gender together. Corresponding odds ratios (ORs) and their 95% confidence interval (95% CI) were estimated as measure of strength of associations, and the level of two-tailed significance was set at  $p < 0.05$ .

## Results

### Sociodemographics and clinical characteristics by gender

A total of 250 patients participated. Their mean age was 32.6 ( $SD = 9.8$ ) years, 52% were females. Only five patients (2%) had received an ADHD-diagnosis before 18 years of age. None had previously received any targeted ADHD treatment or stimulant medication. Table 1 presents socio-demographic and clinical characteristics for all patients and stratified by gender. The females had a significant higher age at referral to the clinic than the males.

**Insert Table 1 about here**

## Sex differences in childhood characteristics (Table 1)

Many patients reported problems with getting involved in fights with peers in childhood (43%) indicating impulsive behavior, a tendency that was significantly more common in males than females (Table 1). A substantial proportion (38%) of all patients had reading or arithmetic skill problems in primary school. These problems were evenly distributed between the sexes, but significantly more males had received assessments by educational psychology services during primary school (39% versus 20%,  $p < 0.01$ ). Regarding severity of childhood symptoms by the WURS, males reported less medical problems in childhood ( $p < 0.01$ ), and more school-related problems ( $p < 0.01$ ) compared to females, but no significant differences in overall childhood ADHD symptom scores were observed between the sexes. Likewise, we did not find any significant sex differences in the number of DIVA assessed childhood ADHD symptoms.

## Sex differences in comorbidity, adult symptoms, education and work status

A large proportion of the total sample had at least one comorbid mental disorder (75%), and 55% had two or more such disorders (not shown in the table). Except for more males having antisocial behavior, we found no significant differences between the sexes (Table 1). A significant proportion of the patients in our sample used or had used a medicine for anxiety or depression in the past year (71%). There was a tendency for more women than men to use such medications (77% versus 65%,  $p < 0.05$ ) which consisted mainly of antidepressants (> 90%), to a lesser degree anxiolytics and sedatives. Such medication was related to higher number of comorbid disorders ( $p < 0.01$ ) (not shown in the tables).

The number of clinician assessed ADHD symptoms in adulthood by the DIVA was significantly higher for females ( $p < 0.01$ ), particularly for inattentive symptoms ( $p < 0.01$ ). Self-reported current ADHD symptoms differed correspondingly with a significant tendency for more frequent symptoms reported by females than males on the ASRS full scale ( $p < 0.01$ ) and the inattentive subscale ( $p < 0.01$ ).

A considerable proportion of the sample (56%) had not completed a secondary school program equivalent to high school; no significant difference between the sexes was observed. However, more males (53%) than females (36%) were in paid work or ordinary studies at enrollment in the study ( $p < 0.01$ ) and more females (58%) were reported with disability or rehabilitation pension than males (41%) ( $p < 0.01$ ) (Table 1).

This sex difference was also reflected in the long term outcome of being disabled for work in the past year (60% of women versus 42% of men,  $p < 0.01$ ).

#### **Insert Table 2 about here**

Factors associated with high school non-completion (Table 3)

Mean age at inclusion into the study was higher among those who had completed high school (35.1,  $SD = 9.7$  years versus 30.2,  $SD = 9.4$  years,  $p < 0.01$ ) (Table 2). Those who did not complete high school more often reported *risk to get into fights with peers*, and a larger proportion had received assessment by educational psychology services during primary school. The non-completers had significantly higher scores on overall child ADHD symptom severity (WURS-25,  $p < 0.01$ ) and had been assessed by the clinicians as having significantly more DSM-IV ADHD symptoms and H/I-symptoms in childhood (DIVA) ( $p = 0.01$ ). No significant differences were found for comorbid mental disorders or ADHD symptoms in adulthood (ASRS) between the two education categories.

#### **Insert Table 3 about here**

Previous assessment by *educational psychology services* during (primary) school and *risk to get into fights with peers* during childhood were significantly associated with *likelihood of not completed high school* when entered one at a time in the regression analyses. After adjusting for sex, these associations remained significant ( $p < 0.05$ ).

The WURS-25 category of ADHD symptom severity ‘high’ (score  $\geq 70$ ) predicted non-completion of high school with OR = 3.0. This indicates a three-fold increased risk of not attaining upper secondary education. Higher numbers of child ADHD H/I-symptoms also remained significantly related to non-completion of high school after adjustment for sex ( $p < 0.01$ ). To control for confounding of disruptive behavior, the number of H/I-symptoms in childhood was entered into the regression-model adjusted for *risk to get into fights with peers* (M.I.N.I.-Plus). With this adjustment, the association to non-completion then became statistically non-significant. However, alternatively adjusting for occurrence of *antisocial-/conduct disorder symptoms* (M.I.N.I.-

Plus), the number of H/I-childhood symptoms maintained statistically significant ( $p < 0.01$ ) as a predictor of high school drop-out (not shown in the tables).

#### Factors associated with work status

The majority of the sample was not in paid work or study (56%) at the time of referral, and 51% had not been in paid work or study in the past year due to disability. Half of the sample also received a disability or rehabilitation pension, reflecting long-term work disability (Table 1). A significantly larger proportion of females (60%) than males (42%) had not been in paid work or study last year (Table 1). The mean age at referral of those *out of work or study* was significantly higher than among those working (Table 2). Overall childhood severity scores by the WURS-25 showed no difference between employed and work disabled patients.

Those who were out of work last year had significantly more comorbid disorders ( $p < 0.01$ ), particularly anxiety disorders in both sexes, and antisocial or conduct disorder among females (8% versus 0%,  $p < 0.01$ ; data not in the tables). A significant proportion of the patients in the group of long-term work disability used or had used a medicine for anxiety or depression in the past year (82%,  $p < 0.01$ ). Those *out of work or study last year* also had significantly higher ASRS inattention scores compared with those in work or study ( $p < 0.01$ ). The patients who were not working also showed a tendency toward having more inattentive symptoms in adulthood ( $p = .04$ ) assessed by DIVA (Table 2).

#### Predicting long term work disability

Higher age at entering the study was significantly related to higher *likelihood of being out of work last year*, and females were more at risk with age adjusted OR = 1.8 in the logistic regression analyses. When adjusting for age and sex, higher numbers of persistent ADHD In- symptoms in adulthood assessed by the DIVA with OR = 1.2 (Table 3), and level of persistent ADHD inattentive symptoms in adulthood measured by the ASRS inattention score with adjusted OR = 1.1 (not shown in the tables), and of the ASRS inattention *high score category* with adjusted OR = 2.5, by categories of the quartiles score; *low* < 24, *high*  $\geq 31$ ) were related to increased likelihood of *being out of work last year* (Table 3). Also, higher *number of comorbid mental disorders* (MINI) remained significantly related to *not being in work last year* with adjusted OR = 1.6 (Table 3). A significant inter-

correlation between number of comorbid disorders and ADHD symptoms (ASRS total score) and inattention symptoms (ASRS inattention score) was found (*Spearman's rho* = 0.22,  $p < 0.01$  and  $rho = 0.19$ ,  $p < 0.01$  respectively). The statistically significant associations found between the ASRS inattention *high score category* and the dependent variable of work disability (Table 3) disappeared when combined with number of comorbid disorders in the regression model (data not shown).

## Discussion

### Main findings

This study examined adult ADHD outcomes of school failure and long term work disability in dimensional relation to previous and persistent ADHD symptoms and comorbidity for both genders. Patients who had more hyperactive and impulsive symptoms and total ADHD symptoms in childhood had a significantly shorter duration of education and an increased risk of drop-out from high school. No significant sex differences were observed concerning these educational outcomes. Work status was weakly related to differences in ADHD characteristics in childhood. In contrast, persistent inattentive ADHD-symptoms in adulthood, as well as the number of comorbid mental disorders in adulthood, were significantly related to an increased risk of long-term work disability. Significantly more women than men were long-term work-disabled.

### Childhood hyperactivity-impulsivity predicted high school drop-out

Longitudinal studies of children with follow up in youth and young adulthood have found adverse educational outcomes associated with the severity of childhood ADHD symptoms (Barbarese et al. 2007; Barkley et al. 1990). Youths with high levels of hyperactive-impulsive symptoms may be more likely to experience negative feedback in school or to make impulsive decisions about discontinuation, than those with fewer symptoms in this domain. However, in contrast to our study, which found that hyperactive-impulsive symptoms, but not conduct disorder, predicted high school dropout, prior studies, found that conduct disorder was the best predictor of high school dropout (Barkley et al. 1990; Breslau et al. 2011). A longitudinal study did not find such an association (Trampush et al. 2009), but lower IQ, reading ability, socioeconomic status, frequent marijuana use, and limited paternal contact significantly differentiated school-dropouts from graduates. Our finding of hyperactivity-

impulsivity in childhood as a predictor of school-failure was modified if adjusted for *risk to get into fights* with peers; and this association became statistically non-significant. However when we adjusted for occurrence of *antisocial-conduct behavior* (M.I.N.I.-Plus), the hyperactive-impulsive childhood symptoms remained a statistically significant predictor of high school drop-out (not shown in the tables), indicating this association was partially independent of antisocial behaviors.

#### Persistent inattentive symptoms related to work disability

While number and severity of ADHD symptoms in childhood were related to lower educational outcomes, these factors seemed not to influence on the outcome of being *out of work last year*. This is in accordance with a report of weak correlations between specific ADHD symptoms and adult impairment (Gordon et al. 2006). However, others found a statistically significant relationship between childhood ADHD symptoms and impairment in adulthood when impairment in broader functional domains was evaluated (Barkley et al. 2006; Kessler et al. 2010; Mannuzza et al. 2011).

We found adult inattentive symptoms to be significantly related to *being out of work last year*. Several studies have reported decreases in hyperactive/impulsive symptoms by age, and persistence of inattentive symptoms into adulthood (Faraone et al. 2006a). Gjervan et al. (2011) also found that current inattentiveness in adults was significantly related to fewer days in ordinary work during the last year. Also according to other authors, the hyperactive/impulsive subtype is less common in adult ADHD (Sobanski et al. 2008), and the inattentive symptom cluster has been reported to be more disabling in ADHD adults (Stavro et al. 2007).

#### Educational and vocational deficits and sex-differences

Almost twice as many (56%) as in the general Norwegian population (33%) of patients in our total sample had not completed high school (Falch et al. 2010) and more than half of the patients had not attained a suitable education for the labor market. However, we did not find any significant association between educational failure and long term work disability. This may be explained partially by existing needs for unskilled workers and employment measures for unskilled or uneducated workers.

The majority of participants were not employed at the time of referral, and half of them had not been in ordinary work or study during the past year due to disability. These disability rates are very high when compared

with the known non-working rate of 18% for the Norwegian population (Statistics Norway, 2012). We found higher non-working rates in our sample than reported in other studies of adults with ADHD (Able et al., 2007; Sobanski et al., 2007), although similar proportions were reported in studies by Halmoy et. al. (2009) and Gjervan et. al. (2011).

Almost twice as many women than men reported long-term unemployment or being fully out of work last year due to disability; this gender difference remained statistically significant when adjusted for age and comorbidity (Table 3). This finding could not entirely be explained by a general trend in the Norwegian population of more women than men working part-time, nor by mental disorders being more common among women (Statistics Norway, 2012) since we compared only those fully out of work, and adjusted for psychiatric comorbidity. This significant sex-difference thus could indicate women to be more susceptible than men in a vocational context to the disabling consequences of ADHD, or that women are more prone to get work environments particularly less compatible with ADHD. This raises unresolved questions about unfavorable environmental work place factors, and proposals for counselling or facilitation.

#### Comorbidity and functional outcomes

Adult comorbidity was significantly related to long-term work disability in our sample, and for both sexes. A large proportion of our sample had psychiatric comorbidity (75%) in accordance with reported prevalences from prior studies of adult ADHD. The total number of comorbid disorders did not differ significantly between the sexes or between those who did and did not complete high-school. Of adult factors with significant relation to long term work outcome, number of comorbid disorders correlated marginally with selected childhood factors, and thus may reflect an independent factor of child ADHD symptoms.

Some studies have shown worse outcome in childhood ADHD with co-occurring psychopathology (Pliszka 1998; Wilens et al. 2002), and similar results have been found for adults with ADHD (McGough et al. 2005; Mick et al. 2008; Weiss et al. 2010). There is a significant literature showing that psychiatric morbidity and anxiety disorders in adults are associated with long term work disability (Lorant et al. 2003; Sareen et al. 2006; Virtanen et al. 2011). A significant proportion of the patients in our sample used or had used a medicine for anxiety or depression last year, and such medication use was associated with long-term work disability. This was expected since those on any medication had a higher number of comorbid disorders. Lack of medical

treatment of comorbidity therefore was unlikely a significantly confounding factor for these worse outcomes, but the issue of ineffective treatment is still not accounted for.

### Strengths and limitations

Our study has several strengths. A novel contribution of the study is the dimensional examination of whether level of disability in adulthood is related to number of childhood criteria met. The sample comprised treatment naïve, adult ADHD patients and represented a wide age-span, both genders and comorbid conditions. We had historical data from school and consultations with former educational psychology services and health care services data. Collateral independent information was collected for the majority of the patients to ascertain childhood data. All patients in the present study were examined with structured diagnostic interviews by trained clinicians and evaluations were not based on self-reported questionnaires or retrospective data only.

A large proportion of the patients were previously undiagnosed concerning ADHD, though many had been recognized with learning difficulties or behavioral problems in childhood. Gjervan et. al. (2012) from Norway reported a higher proportion diagnosed by the age of 18 in their sample (23/149), but Bejerot (2010) from Sweden reported fewer (1/214) with prior diagnosis, as they recruited patients for treatment of first time referred adults with ADHD. Some selection bias that may have contributed to our study is the inclusion criteria of being previously unmedicated, and the fact that more than half of the patients were aged 30 years or older.

However, our findings have to be viewed within the limitations of the design and methods applied. It is a cross-sectional study based on data from a clinical sample. Our findings of statistically significant associations do not imply causal relationships. Furthermore, investigators were not blind to the participants' diagnostic status, which could have influenced their assessments. However, the data from parents and patients were collected independently; parents did not know the ratings of the patients and vice-versa. Still, retrospective data are possibly distorted by current symptoms which may bias estimates of association.

The clinical variables are not presented together in the regression model due to significant inter-correlation. Effects of multi-collinearity were expected to occur in the multivariate analysis, and thus comorbidity as a confounder could not be fully accounted for.

### Conclusions and implications



Severity of ADHD symptoms and a high load of child hyperactive-impulsive symptoms in childhood were associated with drop-out from school and fewer years of attained education, indicating an increased risk for unfavorable educational outcomes related to these symptoms in childhood and adolescence. Persistence of more inattentive symptoms in adulthood was associated with greater occupational impairment and additional adult comorbidity was a major predictor of long term work disability.

Our findings emphasize the serious consequences of ADHD in childhood and adulthood in terms of functional outcomes, and may suggest that early recognition and intervention for ADHD and comorbid mental disorders are of importance to improve the long-term outcome for ADHD patients. Our work further emphasizes the importance of addressing inattentive symptoms in the treatment of adult ADHD and calls for adequate workplace measures to prevent long-term work disability.

**Table 1** Sociodemographic and clinical characteristics by sexes

	Total sample	Females	Males	p
	(n = 250)	(n = 129)	(n = 121)	-
Age, Mean (SD) <sup>b</sup>	32.6 (9.8)	34.1 (9.8)	30.7 (9.5)	< 0.01
<b>School variables, n (%)</b>				
Not completed high school	140 (56)	67 (52)	73 (60)	0.18
Number of years with education, Mean (SD)	11.0 (2.3)	11.3 (2.4)	10.8 (2.1)	0.12
Behavioral risk to get into fights <sup>a</sup>	108 (43)	47 (41)	61 (56)	<b>0.03</b>
Educational psychology services	73 (29)	26 (20)	47 (39)	< 0.01
Lexical or arithmetical skill problems	95 (38)	46 (36)	49 (41)	0.43
<b>Childhood symptoms</b>				
Wender Utah Rating Scale <sup>b</sup> , Mean (SD)				
WURS Medical problems	5.0 (4.4)	5.8 (4.5)	4.0 (4.1)	< 0.01
WURS School-related problems	17.9 (7.6)	16.0 (7.2)	19.8 (7.5)	< 0.01
WURS-25	56.2 (16.8)	55.9 (17.7)	56.2 (16.1)	0.90
WURS-25 category, n (%)				
Low (< 40)	40 (16)	26 (20)	14 (12)	<b>0.05</b>
Moderate (40 - 70)	152 (61)	70 (54)	82 (69)	-
High (≥ 70)	56 (23)	33 (26)	23 (19)	-
Number of ADHD symptoms in childhood (by DIVA <sup>c</sup> ), Mean (SD)				
Total number of symptoms	11.8 (3.1)	11.5 (3.2)	12.2 (2.9)	0.07
Inattention symptoms	6.6 (1.5)	6.5 (1.4)	6.7 (1.6)	0.25
Hyperactivity-impulsivity symptoms	5.2 (2.4)	5.0 (2.5)	5.5 (2.3)	0.11
<b>Adult factors</b>				
Occupational status at inclusion, n (%)				
In paid work or study	111 (44)	47 (36)	64 (53)	< 0.01
Disability or rehabilitation pension	124 (50)	75 (58)	49 (41)	< 0.01
Unemployed	15 (6)	7 (5)	8 (6)	0.69
Work disabled last year	128 (51)	77 (60)	51 (42)	< 0.01
Comorbid mental disorder <sup>a</sup> , n (%)				
Any comorbid mental disorder	188 (75)	96 (74)	92 (76)	0.77
Major depressive episode	59 (24)	32 (25)	27 (22)	0.64
Bipolar disorder	39 (16)	20 (16)	19 (16)	0.97
Anxiety disorder (last year)	136 (54)	77 (60)	59 (49)	0.08
Alcohol use disorder (last year)	38 (15)	16 (12)	22 (18)	0.20
Drug use disorder (last year)	36 (14)	13 (10)	23 (19)	<b>0.04</b>
Antisocial behavior	42 (17)	10 (8)	32 (27)	< 0.01
Number of comorbid disorders <sup>c</sup> , Mean (SD)	1.5 (1.2)	1.5 (1.2)	1.5 (1.2)	0.78
Number of ADHD symptoms in adulthood (by DIVA <sup>c</sup> ), Mean (SD)				
Total number of symptoms (0–18)	12.0 (3.2)	12.5 (3.0)	11.5 (3.3)	< 0.01
Inattention symptoms (0–9)	6.8 (1.7)	7.1 (1.3)	6.5 (2.0)	< 0.01
Hyperactivity-Impulsivity symptoms (0–9)	5.2 (2.3)	5.4 (2.3)	5.0 (2.3)	0.16
Adult ADHD Self-Report Scale (ASRSv1.1), Mean (SD)				
ASRS full scale (0-72)	50.5 (10.2)	51.9 (9.3)	48.8 (10.9)	<b>0.01</b>
Inattention subscale (0-36)	26.9 (5.3)	27.7 (4.6)	26.0 (5.6)	< 0.01
Hyperactivity-impulsivity subscale (0-36)	23.6 (6.6)	24.2 (6.3)	22.8 (7.0)	0.09
Psychopharmacological medication last year (missing = 7), n(%)	173 (71)	96 (77)	77 (65)	<b>0.05</b>

a. By the Mini International Neuropsychiatric Interview (M.I.N.I.), life time if not specified. b. Severity of childhood symptoms rated by the Wender Utah Rating Scale, WURS-25 category by the quartiles: WURS-25 score < 40 → 0 (ref.). c. The structured Diagnostic Interview for ADHD in adults, second edition (DIVA 2.0); number of symptom criteria met in childhood and adulthood assessed separately by the clinicians.

**Table 2** Characteristics and symptoms by high school drop-out and long term work disability \*

	High school drop-out	Completed high school	<i>p</i> <sup>a</sup>	Work disabled	Employable last year	<i>p</i> <sup>a</sup>
	(n = 140)	(n = 110)		(n = 128)	(n = 122)	
<b>Age, Mean (SD)</b> <sup>b</sup>	30.2 (9.4)	35.1 (9.7)	< <b>0.01</b>	34.3 (9.8)	30.6 (9.5)	< <b>0.01</b>
<b>Education, n (%)</b>						
Risk to get into fights <sup>c</sup>	68 (56)	40 (39)	<b>0.01</b>	58 (50)	50 (45)	0.42
Educational psychology services	50 (36)	23 (21)	<b>0.01</b>	34 (27)	32 (27)	0.98
Lexical or arithmetical skill problems	55 (40)	40 (37)	0.64	53 (41)	42 (35)	0.30
Not completed high school	-	-	-	76 (59)	64 (53)	0.27
Number of years with education, Mean (SD) <sup>b</sup>	9.4 (0.7)	13.1 (2.0)	< <b>0.01</b>	10.8 (2.0)	11.3 (2.6)	0.08
<b>The Wender Utah Rating Scale <sup>c</sup>, Mean (SD) <sup>b</sup></b>						
WURS Medical problems	5.0 (4.7)	5.0 (4.1)	0.96	5.5 (4.8)	4.4 (3.9)	<b>0.04</b>
WURS School-related problems	18.6 (7.5)	16.8 (7.7)	0.07	17.8 (7.6)	17.8 (7.6)	0.95
WURS-25	58.7 (18.0)	52.7 (14.9)	< <b>0.01</b>	57.0 (16.4)	55.0 (17.5)	0.34
WURS-25 category <sup>a</sup> , n (%)						
Low (< 40)	20 (15)	20 (18)	< <b>0.01</b>	17 (13)	23 (19)	0.48
Moderate (40 - 70)	76 (55)	76 (69)	-	80 (63)	72 (60)	-
High (≥ 70)	42 (30)	14 (13)	-	30 (24)	26 (22)	-
<b>Number of ADHD symptoms in childhood <sup>d</sup>, Mean (SD) <sup>b</sup></b>						
Total number	12.4 (2.9)	11.1 (3.2)	< <b>0.01</b>	11.5 (3.2)	12.1 (3.0)	0.11
Inattention	6.8 (1.4)	6.4 (1.6)	<b>0.04</b>	6.5 (1.5)	6.6 (1.5)	0.54
Hyperactivity-impulsivity	5.6 (2.3)	4.7 (2.5)	< <b>0.01</b>	5.0 (2.6)	5.5 (2.1)	0.09
<b>Comorbid disorders <sup>e</sup>, n (%)</b>						
Depressive disorder	13 (9)	18 (16)	0.09	15 (23)	16 (10)	0.72
Bipolar disorder	21 (15)	18 (16)	0.77	25 (20)	14 (12)	0.08
Anxiety disorder (last year)	79 (56)	57 (52)	0.47	82 (64)	54 (44)	< <b>0.01</b>
Alcohol use disorder (last year)	26 (19)	12 (11)	0.09	20 (16)	18 (15)	0.85
Drug use disorder (last year)	23 (16)	13 (12)	0.30	20 (16)	16 (13)	0.57
Antisocial or conduct behaviour	25 (18)	17 (16)	0.60	23 (18)	19 (16)	0.59
<b>Number of comorbid disorders <sup>d</sup>, Mean (SD) <sup>b</sup></b>	1.5 (1.1)	1.4 (1.2)	0.36	1.8 (1.2)	1.2 (1.1)	< <b>0.01</b>
<b>Number of ADHD symptoms in adulthood <sup>d</sup>, Mean (SD) <sup>b</sup></b>						
Total number of symptoms (0–18)	12.2 (3.2)	11.8 (3.1)	0.28	12.2 (3.1)	11.8 (3.4)	0.35
Inattention (0–9)	7.0 (1.8)	6.6 (1.6)	0.07	7.0 (1.4)	6.6 (1.9)	<b>0.04</b>
Hyperactivity-impulsivity (0–9)	5.3 (2.3)	5.2 (2.2)	0.84	5.2 (2.3)	5.3 (2.2)	0.84
<b>Adult ADHD Self-Report Scale, Mean (SD) <sup>b</sup></b>						
ASRS full scale (0-72)	51.0 (10.7)	49.7 (9.4)	0.31	51.2 (10.2)	49.6 (10.1)	0.21
Inattention subscale (0-36)	27.3 (5.5)	26.4 (4.9)	0.14	27.4 (4.8)	26.0 (5.6)	<b>0.01</b>
Hyperactivity-impulsivity subscale (0-36)	23.6 (6.8)	23.3 (6.6)	0.70	23.4 (7.0)	23.5 (6.4)	0.90
<b>Psychopharmaca last year, n (%)</b>	91 (68)	82 (75)	0.21	103 (82)	70 (60)	< <b>0.01</b>
(not ADHD-medication) (missing = 7)						

\*Patients classified by completed high school or not (lower education) and being out of work or study last year by disability.  
a. From Pearson chi-square, 2-sided test if not otherwise specified. b. *t* test, independent groups, 2-sided if not otherwise specified.  
c. Severity of childhood symptoms rated by the Wender. Utah Rating Scale WURS-25 category by the quartiles: WURS-25 score < 40 → 0 (low = ref). d. The structured Diagnostic Interview for ADHD in adults, second edition (DIVA 2.0), number of symptom criteria met in childhood and adulthood assessed separately. e. The Mini International Neuropsychiatric Interview (M.I.N.I.) plus version for DSM-IV, lifetime if not otherwise specified.

**Table 3** Prediction of adult functional outcome unadjusted and adjusted for age and sex by logistic regression analyses

	Low education		Work disability	
	Likelihood of 'not completed high school' <sup>a</sup>		Likelihood of 'being out of work last year' <sup>a</sup>	
(N = 250)	Unadjusted OR (CI)	Adjusted OR (CI)	Unadjusted OR (CI)	Adjusted OR (CI)
Age (years)	not in equation	not in equation	<b>1.04 (1.01 - 1.07)**</b>	<b>1.04 (1.01 - 1.06)**</b>
Sex				
Male	1.0	ref.	1.0	ref.
Female	0.7 (0.43 - 1.17)	0.7 (0.43 - 1.17)	<b>2.0 (1.23 - 3.36)**</b>	<b>1.8 (1.10 - 3.08)*</b>
Childhood factors				
Educational psychology services	<b>2.1 (1.18 - 3.74)*</b>	<b>0.5 (0.28 - 0.90)*</b>	1.0 (0.56 - 1.68)	not in equation
Risk to get into fights (M.I.N.I. <sup>b</sup> )	<b>2.0 (1.18 - 3.43)**</b>	<b>1.9 (1.14 - 3.34)*</b>	0.8 (0.48 - 1.36)	-
WURS-25 category <sup>c</sup>				
Low category (< 40)	1.0	ref.	1.0	-
Moderate (40 - 70)	1.0 (0.50 - 2.01)	0.9 (0.46 - 1.88)	1.5 (0.74 - 3.03)	-
High (≥ 70)	<b>3.0 (1.26 - 7.13)**</b>	<b>3.0 (1.24 - 7.05)**</b>	1.5 (0.69 - 3.54)	-
WURS Medical	1.0 (0.94 - 1.06)	not in equation	<b>1.1 (1.002 - 1.13)*</b>	1.0 (0.99 - 1.11)
Number of ADHD Hyperactive-Impulsive-symptoms in childhood <sup>d</sup>	<b>1.2 (1.05 - 1.30)**</b>	<b>1.1 (1.01 - 1.26)*</b>	0.9 (0.82 - 1.02)	not in equation
Adult factors				
Comorbid disorders <sup>b</sup>	not in equation	not in equation	<b>1.6 (1.28 - 2.04)***</b>	<b>1.6 (1.27 - 2.06)***</b>
Number of persistent ADHD	-	-	<b>1.2 (1.005-1.36)*</b>	<b>1.2 (1.002-1.38)*</b>
Inattention symptoms in adulthood <sup>d</sup>				
ASRS Inattention Score <sup>e</sup>				
Low category (< 24)	-	-	1.0	ref.
Moderate (24 - 31)	-	-	1.5 (0.86 - 2.77)	1.5 (0.81 - 2.73)
High (≥ 31)	-	-	<b>2.7 (1.26 - 5.59)**</b>	<b>2.5 (1.16 - 5.38)*</b>

a. Logistic Regression, specified variables entered in the equation, unadjusted Odds Ratio (OR) estimated by entering factors one at a time in the equation. Probability stepwise for entry .05, removal .10. Education status is adjusted only for gender, work status is adjusted for age and gender.  
b. Number of disorders by the Mini International Nevropsychiatric Interview (M.I.N.I.) plus version for DSM-IV. c. WURS-25 category: WURS-25 score < 40 → low (ref.), score between 40 - 70 → moderate and score ≥ 70 → high. d. Number of ADHD symptoms by DIVA (DSM-IV ADHD criteria) of childhood and adulthood assessed separately. e. Adult ADHD Self report Scale, subscale of 9 ADHD inattentive symptoms (score range 0 - 36) ; inattention category by quartiles: score < 24 → low (ref.). \**p* < 0.05, \*\**p* < 0.01, \*\*\**p* < 0.001, OR (CI: 95%), logistic regression, sig. 2-tailed.

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